**Annals of Clinical and Analytical Medicine**
*Original Research*

# Effect of vitamin D deficiency on ocular blood flow

Vitamin D deficiency and ocular blood flow

Ayşe Güzin Taşlıpınar Uzel[1], Özlem Ünal[2], Demet İyidoğan[3], Elif Şimşek Ürer[4], Nagihan Uğurlu[5], Mehmet Murat Uzel[6]
[1] Department of Ophthalmology, Faculty of Medicine, Ufuk University, Ankara
[2] Department of Radyology, Ankara State Hospital, Ankara
[3] Antalya Dünya Göz Hospital, Antalya
[4] Samsun Physical Therapy and Rehabilitation Hospital, Samsun
[5] Department of Ophthalmology, Faculty of Medicine, Yıldırım Beyazıt University, Atatürk Education and Research Hospital, Ankara
[6] Department of Ophthalmology, Faculty of Medicine, Balikesir University, Balikesir, Turkey

*This study was presented as an oral presentation at the 53rd National Congress of the Turkish Ophthalmology Association, Turkey, 2019*

**Abstract**

Aim: In this study, we aimed to evaluate the effects of vitamin D deficiency (VDD) on retrobulbar blood flow in healthy eyes.

Material and Methods: In this prospective study, thirty eyes of 30 patients with VDD (Group 1) and 25 eyes of 25 individuals without VDD (Group 2) were included. The peak systolic flow velocity (PSV), end-diastolic flow velocity (EDV) and vascular resistance index (RI) were obtained from the ophthalmic artery (OA) with color doppler imaging. Multiple linear regression was performed for the covariate-adjusted comparison.

Results: Mean ages were 37.83±9.89 years in Group 1 and 35.32±9.61 years in Group 2, (p = 0.347). Mean values of serum 25(OH)D3 level were 11.38 ± 3.85 ng/dl in Group 1 and 26.80 ± 10.03 ng/dl in Group 2 (p < 0.001). PSV and EDV were significantly higher in Group 2 than in Group 1 (p<0.001, p=0.001, respectively). RI was slightly higher in Group 1 than in Group 2, but this difference was not statistically significant. In multivariate linear regression, PSV and EDV were positively correlated with OPP, and negatively affected by the presence of VDD.

Discussion: VDD can be an important factor in reducing ocular blood flow.

**Keywords**

Vitamin D Deficiency, Color Doppler Imaging, Retrobulbar Blood Flow, Ophthalmic Artery, Multiple Linear Regression

DOI: 10.4328/ACAM.21343 Received: 2022-08-05 Accepted: 2022-09-21 Published Online: 2022-09-29 Printed: 2022-10-01 Ann Clin Anal Med 2022;13(10):1158-1161
Corresponding Author: Ayşe Güzin Taşlıpınar Uzel, Department of Ophthalmology, Faculty of Medicine, Ufuk University, Dr. Rıdvan Ege Hospital, Ankara, Turkey.
E-mail: agtaslipinar@gmail.com P: +90 312 204 40 00
Corresponding Author ORCID ID: https://orcid.org/0000-0002-0079-5179

## Introduction

Vitamin D is well known for its role in calcium and phosphorus metabolism, which are important in regulation of the musculoskeletal system [1]. However, its effects on cell proliferation and differentiation, apoptosis, immunity, and angiogenesis have recently been studied [2]. Vitamin D deficiency (VDD) is also associated with cardiovascular diseases [3]. The inhibitory effects of vitamin D on the renin-angiotensin-aldosterone system (RAAS) and its protective effects on the vessels are among the physiopathological mechanisms explaining this association [4]. Additionally, due to the effects of vitamin D on arterial compliance and endothelium, arterial stiffness increases and blood flow is affected in VDD [5].

Recent research on the effect of VDD on eye disorders has established a link between the severity of diseases such central retinal vein occlusion, glaucoma, uveitis, diabetic retinopathy, and age-related macular degeneration and VDD [6-9]. Although the underlying mechanism is not fully known, VDD has been shown to affect retinal and choroidal microvasculature in healthy individuals [10, 11]. It is unclear whether these changes are the result of a specific local effect or a general decline in ocular blood flow. Changes in ocular perfusion also play an important role in the pathogenesis of many ocular diseases [12,13]. Therefore, the effect of VDD on blood flow is an issue that needs to be emphasized in order to understand its effect on ocular diseases.

The aim of the study is to evaluate the effects of VDD on ophthalmic artery (OA) by measuring the peak systolic flow velocity (PSV), end-diastolic flow velocity (EDV) and vascular resistance index (RI) in healthy eyes.

## Material and Methods

This prospective study was conducted between March 2016 and May 2016 at Ankara Atatürk Training and Research Hospital in accordance with the tenets of the Declaration of Helsinki. The protocol was approved by the Yildirim Beyazit University Ethics Committee. Informed consent was obtained from all individual participants included in the study.

Serum 25-hydroxyvitamin D3 (25(OH)D3) concentrations were measured by high-performance liquid chromatography. Vitamin D levels below 20 ng/ml were considered as VDD (Group 1), according to the guidelines of the U.S. Institute of Medicine [14]. Healthy volunteers whose serum vitamin D levels were above 20 ng/ml were included as a control group (Group 2). Patients younger than 18 years or with a history of ocular trauma and intraocular surgery, uveitis, glaucoma and retinal pathologies, systemic disease, smoking and/or current pregnancy were excluded from the study.

All participants underwent a complete ophthalmological examination, including measurement of intraocular pressure (IOP) with a Goldmann applanation tonometer.

The weight and height of the participants were appropriately measured by the same device for all cases. After obtaining body weight (in kilograms) and height (in meters) values, BMI was calculated using the weight/height2 (kg/m2) formula.

All patients rested for half an hour and, caffeinated beverages and alcohol consumption were questioned before measurements of arterial blood pressure (BP), and color Doppler imaging was performed. BP was measured using a sphygmomanometer. Mean arterial pressure (MAP) was calculated as follows: 1/3 systolic BP + 2/3 diastolic BP. Similarly, mean ocular perfusion pressure (OPP) was calculated as 2/3 MAP - IOP.

Retrobulbar blood flow was measured with a high-frequency linear probe (12-17 MHz) on an Aplio 500 ultrasound machine (Toshiba Medical Systems, Co., LTD, Otawara, Japan). After applying a sterile gel to the outside of the eyelid of the patient lying in the supine position with his eyes closed, a gray scale examination followed by a color Doppler imaging examination was performed without applying pressure. A radiologist, who was blinded to the vitamin D levels of the participants, took measurements from OA at the same time of day. Measurements were made at an angle set parallel to the direction of blood flow and, the peak systolic flow velocity (PSV) and end-diastolic flow velocity (EDV) were evaluated. The vascular resistance index (RI) was calculated by using the formula of RI=(PSV-EDV)/PSV. [14] The right eyes of the participants were analyzed.

A priori power analysis using PASS 11 (Power and Sample Size Calculation Software, Version 11) revealed that we required to enroll at least 25 eyes for each group in the study. In the present study, 30 eyes were included in the study group and 25 eyes in the control group and, accordingly, the power of the study was 82.3%.

Data were analyzed using the SPSS software (version 21; International Business Machines Co., Armonk, NY). The variables were presented as mean and standard deviation. The normality of all data was evaluated with the Shapiro-Wilk test. Differences between the groups were analyzed with the independent samples t-test. Multiple linear regression was performed for the covariate-adjusted comparison. P values < 0.05 were accepted as statistically significant.

## Results

The mean age was 37.83±9.89 years in Group 1 and 35.32±9.61 years in Group 2 (p=0.347). The gender ratio was also similar between the groups (18/12 in group 1, 16/9 in group 2, p=0.491). The mean serum 25(OH)D3 levels were 13.52±6.88 ng/ml and 24.08±7.14 ng/ml in Group 1 and Group 2, respectively (p <0.001). BMI was slightly higher in Group 1 (26.20±1.74 kg/m2) than in Group 2 (25.36±1.77 kg/m2), but this difference was not statistically significant (p=0.084).

As shown in Table 1, OPP did not differ between groups (p=0.163), but PSV and EDV were significantly higher in Group 2 than in Group 1 (p<0.001, p=0.001 respectively). RI was slightly higher in Group 1 than in Group 2, but this difference was not statistically significant.

The multivariate linear regression analysis between ocular

**Table 1.** Baseline characteristics of the subjects

| | Group 1 (n=30) | Group 2 (n=25) | P value |
|---|---|---|---|
| OPP (mm Hg) | 44.81±2.57 | 43.77±2.89 | 0.163 |
| PSV(cm/s) | 29.15±3.84 | 33.74±4.81 | <0.001 |
| EDV(cm/s) | 7.94±1.70 | 9.82±2.07 | 0.001 |
| RI | 0.72±0.03 | 0.70±0.05 | 0.099 |

OPP: ocular blood pressure, PSV: peak systolic flow, EDV: end diastolic volume, RI: resistance index

**Table 2.** Multivariate linear regression analysis between retrobulbar blood flow and other variables including Vitamin D

| | PSV(cm/s) | | EDV(cm/s) | | RI | |
|---|---|---|---|---|---|---|
| | B coefficient (SE) | P value | B coefficient (SE) | P value | B coefficient (SE) | P value |
| Age (years) | -0.11 (0.04) | 0.007 | -0.09 (0.02) | <0.001 | 0.002 (0.001) | 0.002 |
| Gender | 0.22 (0.75) | 0.765 | 0.02 (0.40) | 0.950 | 0.001 (0.012) | 0.980 |
| Presence of VDD | -5.40 (0.78) | <0.001 | -1.87 (0.42) | <0.001 | 0.010 (0.010) | 0.264 |
| OPP (mm Hg) | 1.4 (0.15) | <0.001 | 0.21 (0.08) | 0.012 | 0.003 (0.002) | 0.222 |
| BMI ($kg/m^2$) | 0.02 (0.21) | 0.924 | 0.01 (0.11) | 0.949 | 0.001 (0.003) | 0.965 |

PSV: peak systolic flow velocity, EDV: end diastolic volume, RI: resistance index , VDD: vitamin D deficiency, OPP: ocular blood pressure, BMI: body mass index,

perfusion parameters and demographic variables, OPP, BMI and presence of VDD is presented in Table 2. No correlation was found between gender, BMI, and ocular perfusion parameters, but age showed a statistically significant correlation with PSV, EDV and RI. While PSV and EDV were positively correlated with OPP, they were negatively affected by the presence of VDD.

## Discussion

The present study revealed that ocular perfusion is negatively affected in presence of VDD. Other related factors with EDV and PSV are age and OPP.

The role of VDD in many diseases associated with vascular pathologies has been studied. Especially, relationship between VDD and cardiovascular diseases has been demonstrated. Kendrick et al. reported that patients with VDD had more angina, myocardial infarction and heart failure [15]. In recent years, studies have shown that VDD is associated with many eye diseases. Kim et al. have reported that low serum vitamin D status is associated with increased glaucoma risk in females [8]. Studies have shown that VDD accelerates the development of neovascularization and proliferative retinopathy in patients with type 2 diabetes mellitus [16, 17]. Parekh et al. have shown a correlation between reduced serum vitamin D levels and risk for early age-related macular degeneration [18]. A meta-analysis found a trend for late AMD among patients with VDD. [7]. In elderly patients without macular dysfunction, VDD is also associated with thinning of macular thickness [19].

In our study, we found that the blood flow decreased significantly in the group with VDD. One of the underlying mechanisms may be RAAS activation. It has been shown that vitamin D modulates RAAS. Renin expression was significantly increased in vitamin D receptor knock-out mice and suppressed in wild type mice after injecting 1.25 (OH)2D [20]. Activation of RAAS leads to severe vasoconstriction. Another factor can be acceleration of atherosclerosis due to VDD. VDD has been associated with increased pro-inflammatory cytokines such as TNF-α, interleukin (IL) -6 and interleukin-1beta (IL-1β), which predisposes to the development of atherosclerosis [21]. This condition is associated with atherosclerosis. In addition, vitamin D has been shown to reduce the risk of atherosclerosis by decreasing endoplasmic reticulum stress and oxidative stress, and thus has a protective effect on endothelial cells [22]. VDD increases arterial stiffness and atherosclerosis and also affects blood flow [5]. Influence of changes in ocular blood flow in the occurrence and progression of these diseases might suggest that VDD worsens these diseases by affecting ocular blood flow. Both changes in structure of artery and its regulation affect arterial stiffness and blood flow.

Vascular function varies with aging and may affect the retrobulbar blood flow. The most important cause of altered vascular function in elderly individuals is impaired endothelial function [23]. In addition, atherosclerosis, which increases with age, is another important factor [24]. Another result of our study is that low OPP values reduce retrobulbar blood flow. Low OPP is thought to be a risk factor for glaucoma [25]. However, it is not clear which mechanism causes this. In particular, low perfusion in the optic nerve head may increase glaucomatous damage.

This is the first study to evaluate the effects of VDD on ocular perfusion. However, there were some limitations in our study. We carried out the study in the spring to evaluate average levels of serum vitamin D. However, cross-sectional measurement of vitamin D levels might be misleading when assessing VDD. Fluctuation of level of serum vitamin D in a year or throughout years might cause different effects on ocular blood flow. Cohort studies in which vitamin levels are monitored for longer periods are needed, and assessment of vitamin D levels in different seasons might also be beneficial in evaluating the effects of VDD.

## *Conclusion*

The relationship between VDD and various eye diseases has been frequently investigated in recent years. Ocular perfusion reduction in VDD may be an important factor in the emergence or aggregation of these diseases.

***Scientific Responsibility Statement***

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.*

***Animal and human rights statement***

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.*

***Funding:*** *None*

***Conflict of interest***

*None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.*

***References***

*1. Bouillon R, Marcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, et al. Skeletal and Extraskeletal Actions of Vitamin D: Current Evidence and Outstanding Questions. Endocr Rev. 2019;40(4):1109-51.*

*2. Nebbioso M, Buomprisco G, Pascarella A, Pescosolido N. Modulatory Effects of 1,25-dihydroxyvitamin D3 on Eye Disorders: A Critical Review. Critical Reviews in Food Science and Nutrition. 2017; 57(3):559-65.*

*3. Cosentino N, Campodonico J, Milazzo V, De Metrio M, Brambilla M, Camera M, et al. Vitamin D and Cardiovascular Disease: Current Evidence and Future Perspectives. Nutrients. 2021;13(10):3603*

*4. De la Guía-Galipienso F, Martínez-Ferran M, Vallecillo N, Lavie CJ, Sanchis-Gomar F, Pareja-Galeano H. Vitamin D and cardiovascular health. Clin Nutr. 2021;40(5):2946-57.*

*5. Lee JH, Suh HS. Association of serum 25-hydroxy-vitamin D Concentration and arterial stiffness among Korean adults in single center. J Bone Metab. 2017;24(1):51-8.*

*6. Epstein D, Kvanta A, Lindqvist PG. Vitamin D Deficiency in Patients with Central*

*Retinal Vein Occlusion: A Case Control Study. Curr Eye Res. 2017;42(3):448-51.*
*7. Ferreira A, Silva N, Furtado MJ, Carneiro Â, Lume M, Andrade JP. Serum vitamin D and age-related macular degeneration: Systematic review and meta-analysis. Surv Ophthalmol. 2021;66(2):183-97.*
*8. Kim HT, Kim JM, Kim JH, Lee MY, Won YS, Lee JY, et al. The Relationship between Vitamin D and Glaucoma: A Kangbuk Samsung Health Study. Korean J Ophthalmol. 2016;30(6):426-33.*
*9. Tecilazich F, Formenti AM, Giustina A. Role of vitamin D in diabetic retinopathy: Pathophysiological and clinical aspects. Rev Endocr Metab Disord. 2021;22(4):715-27.*
*10. Icel E, Ucak T, Ugurlu A, Erdol H. Changes in optical coherence tomography angiography in patients with vitamin D deficiency. Eur J Ophthalmol. 2022; DOI: 10.1177/11206721221086240.*
*11) Vural E, Hazar L, Çağlayan M, Şeker Ö, Çelebi ARC. Peripapillary choroidal thickness in patients with vitamin D deficiency. Eur J Ophthalmol. 2021;31(2):578-83.*
*12. Kayser S, Vargas P, Mendelsohn D, Han J, Bi H, Benavente A, et al. Reduced Central Retinal Artery Blood Flow Is Related to Impaired Central Visual Function in Retinitis Pigmentosa Patients. Curr Eye Res. 2017; 14:1-8.*
*13. Shab GB, Sharma S, Mehta AA, Goyal RK. Oculohypotensive effect of angiotensin-converting enzyme inhibitors in acute and chronic models of glaucoma. J Cardiovasc Pharmacol. 2000; 36(2):169-75.*
*14. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011; 96(1):53-8.*
*15. Kendrick J, Targher G, Smits G, Chonchol M. 25 Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey. Atherosclerosis. 2009;205(1):255-60*
*16. Mohammadian S, Fatahi N, Zaeri H, Vakili MA. Effect of vitamin d3 supplement in glycemic control of pediatrics with type 1 diabetes mellitus and vitamin d deficiency. J Clin Diagn Res. 2015; 9(3):5-7.*
*17. Jung CH, Kim KJ, Kim BY, Kim CH, Kang SK, Mok JO. Relationship between microvascular complications and vitamin D deficiency in type 2 diabetes mellitus. Nutr Res. 2016; 36:117-24.*
*18. Parekh N, Chappell RJ, Millen AE, Albert DM, Mares JA. Association between vitamin D and age-related macular degeneration in the Third National Health and Nutrition Examination Survey, 1988 through 1994. Arch Ophthalmol. 2007; 125(5):661-9.*
*19. Graffe A, Beauchet O, Fantino B, Milea D, Annweiler C. Vitamin D and Macular Thickness in the elderly:an optical coherence tomography study. IOVS. 2014; 55(8):5298-303.*
*20. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Investig. 2002;110(2):229–38.*
*21. Gupta GK, Agrawal T, Rai V, Del Core MG, Hunter WJ 3rd, Agrawal DK. Vitamin D Supplementation Reduces Intimal Hyperplasia. Restenosis following Coronary Intervention in Atherosclerotic Swine. PLoS One. 2016;11(6):e0156857.*
*22. Haas MJ, Jafri M, Wehmeier KR, Onstead-Haas LM, Mooradian AD. Inhibition of endoplasmic reticulum stress and oxidative stress by vitamin D n endothelial cells. Free Radiac Biol Med. 2016;99:1-10*
*23. Olive JL, DeVan AE, McCully KK. The effects of aging and activity on muscle blood flow. Dyn Med. 2002;1:2.*
*24. Wang JC, Bennett M. Aging and atherosclerosis: mechanisms, functional consequences, and potential therapeutics for cellular senescence. Circ Res. 2012;111(2):245-59.*
*25. Cherecheanu AP, Garhofer G, Schmidl D, Werkmeister R, Schmetterer L. Ocular perfusion pressure and ocular blood flow in glaucoma. Curr Opin Pharmacol. 2013;13(1):36-42*

***How to cite this article:***
***Ayşe Güzin Taşlıpınar Uzel, Özlem Ünal, Demet İyidoğan, Elif Şimşek Ürer, Nagihan Uğurlu, Mehmet Murat Uzel.*** *Effect of vitamin D deficiency on ocular blood flow. Ann Clin Anal Med 2022;13(10):1158-1161*