Original Article

Emerging role of vitamin D deficiency as a risk factor for retinal venous occlusions and need for public health measures for its prevention

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Abstract

Purpose: To estimate levels of serum vitamin D in patients of retinal vein occlusion (RVO) and compare with age- and sex-matched controls. **Methods:** A prospective case-control study of 54 patients of RVO and 54 age- and sex-matched attendants of patients presenting to a tertiary care hospital in Delhi was performed. Patients on vitamin D supplementations and RVO due to infective or immunological causes or patients of glaucoma were excluded. Serum vitamin D levels of all the study participants along with relevant blood investigations with history and examination were documented. Vitamin D deficiency was defined as <20 ng/ml. **Results:** The mean serum vitamin D levels seen in RVO patients and the control group were 14.19 ± 5.23 ng/ml and 19.42 ± 10.27 ng/ml, respectively (*P* value = 0.001) with an odds ratio of 10.558 (CI = 2.34–47.50), indicating vitamin D deficiency to be strongly correlated with RVO. Maximum patients of RVO (46.3%) were seen during the winter season. The study noted hypertension [odds ratio 20.22 (CI = 5.812–70.347)], dyslipidemia, and anemia [odds ratio 4.107 (CI = 0.62–26.90)] to be the risk factors for RVO as previously proved in the literature. Smoking, diabetes, alcohol intake, and body mass index did not emerge as risk factors for RVO. **Conclusion:** Vitamin D deficiency is associated with RVO; hence, estimation of serum vitamin D levels should be advised as a part of routine investigations while looking for the cause of RVOs. Public health measures like food fortification with vitamin D micronutrients and public awareness towards increased sunlight exposure in the community are simple, inexpensive measures that can decrease the burden of sight-threatening disease of RVO in the community.

Keywords: Public health measures, risk factors, retinal vein occlusion, vitamin D deficiency

Introduction

Retinal vein occlusion (RVO) is an important sight-threatening retinal vascular disorder affecting as many as 28.06 million people globally as estimated in 2015.[1] Based on anatomical location, it can be classified into central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), and hemi-retinal vein occlusion (HRVO). The known risk factors for RVO are systemic diseases like hypertension (HTN), diabetes mellitus (DM), dyslipidemia, and other known hypercoagulable disorders including hyperhomocysteinemia and intraocular pathologies like glaucoma and vasculitis.

Recently, research and data have been published to show the association of low vitamin D levels with thrombosis and venous occlusions. Vitamin D binds to vitamin D-binding protein and gets transported to target organs. Here, it is a natural ligand to

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vitamin D receptors to enable their biological actions. There are several clinical reports corroborating vitamin D deficiency with an increase in thrombotic episodes.[2–4] This implicates the role of vitamin D in the causation of thrombosis-related pathways.

Multiple studies have shown a positive correlation between vitamin D deficiency and vascular diseases like HTN, coronary heart disease, and cerebrovascular accidents.[5–8] Also, improvement in vascular endothelial function has been noted with vitamin D supplementation, indicating the importance of vitamin D in vascular disorders.[9,10]

In some cases of RVO, when no cause is found, they are labeled as idiopathic. The list of identifiable risk factors for RVO is still incomplete. Considering the above association of vitamin D deficiency and vascular disorders, these idiopathic cases of RVO may be related to reduced levels of vitamin D. We conducted this study at our tertiary care centre in North India to evaluate serum levels of vitamin D in patients of RVO presenting to our hospital to determine any association between the two. Very few studies have been published on the evaluation of vitamin D levels in RVO, and hence, there is a lacuna of knowledge regarding this association which we aim to study.[11–14]

Vitamin D is a micro-nutrient and forms a part of nutrition for an individual. General physicians advise on adequate nutrition and preventive measures against diseases. Evaluation of serum vitamin D and its association with the sight-threatening RVOs can guide physicians towards the importance of public awareness, public health measures, and routine estimation of serum vitamin D levels with the aim to improve vitamin D levels in the community.

Materials and Methods

This case-control study was approved by the institutional ethics committee and adhered to the Declaration of Helsinki. A total of 54 cases (age group 40–80 years) with the first episode of RVO presenting to our hospital (one of the largest tertiary care centres of North India) within 3 months of the onset of RVO were enrolled after informed consent. They were compared with 54 age- and sex-matched controls who were attendants of patients as they had comparable dietary and socioeconomic conditions. Patients on vitamin D supplementations and RVO due to infective or immunological causes or patients of glaucoma were excluded.

All recruited patients underwent a detailed history and ophthalmic examination including fundus photographs, optical coherence tomography, and fundus fluorescein angiography wherever required. Systemic examinations like details of the history of HTN, DM, smoking, alcohol intake, and other predisposing factors were also noted.

After overnight fasting (12 hours), a blood sample was collected in a plain vial and was stored at -20 degrees Celsius. The serum from this vial was used for vitamin D estimation by the Chemiluminiscent Immunoassay kit (CLIA). Also, hemograms, blood sugars, and lipid profiles were assessed and standard procedures for calculation of body mass index (BMI) were done for all patients.[15]

Vitamin D deficiency was defined as serum levels of <20 ng/ml.[16] The seasons were defined as Summer (March–June), Monsoon (July–September), Autumn (October–November), and Winter (December–February).[17]

Qualitative variables were analysed using Chi-square test or Fisher's exact test wherever applicable. Quantitative variables were analysed using the independent *t*-test. Univariate and multivariate logistic regressions were used to find out significant risk factors of RVO. Data entry was done in Microsoft EXCEL, and the final analysis was done with Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 25.0. For statistical significance, a *P* value of less than 0.05 was considered statistically significant.

Results

The study included 54 cases of RVO [17 patients (31.5%) CRVO, 35 patients (64.8%) BRVO, and 2 patients (3.7%) HRVO] and 54 age- and sex-matched controls. The mean age for cases and control group was 60.22 years ± 6.44 and 60.83 years ± 7.02, respectively (*P* value > 0.05). RVO was seen more in the age group of 61–70 years (48.1%) [Table 1]. Twenty-four (44.4%) were male and 30 (55.6%) females in each group (*P* value > 0.05) [Table 1]. A higher number of RVO cases was seen in the winter season, 25/54 (46.3%) [Table 2].

Serum vitamin D was deficient (<20 ng/ml) in both cases [48/54 (88.9%)] and controls [30/54 (55.6%)]. The mean serum levels of vitamin D in both groups were low, cases (14.19 ± 5.23 ng/ml) and controls (19.42 ± 10.27 ng/ml) [Table 3]. The above two differences were statistically significant, *P* value < 0.001 [Tables 1 and 3]. Mean serum vitamin D levels were noted to be lower in all age groups of cases compared to controls, but this difference was statistically significant in the age group of 61–80 years (*P* value = 0.007). This group was noted to have a higher number of RVO cases [Table 1]. On multivariate logistic regression analysis, serum vitamin D deficiency (<20 ng/ml) had an odds ratio of 10.558 (95% CI = 2.346–47.509), indicating that vitamin D deficiency is a risk factor for RVO. That is, more the vitamin D deficiency, higher is the risk of RVO [Table 4].

Out of 54 cases, 44 (81.5%) had hypertension compared to the control group having 12/54 (22.2%) with hypertension disease (*P* value = <0.001) [Table 1]. The odds ratio calculated for hypertension was 20.221 (95% CI = 5.812–70.347), indicating that hypertension is strongly associated with the development of RVO [Table 4]. To overcome hypertension as a confounding risk factor, serum vitamin D was compared in hypertensive and

Table 1: Profile of patients in the study

Parameter	Cases (%)	Controls (%)	*P*
Number	54	54	
Age			
Mean±SD (years)	60.22±6.44	60.83±7.02	>0.05
40-50 years (*n*)	4 (7.4%)	6 (11.1%)	
51-60 years (*n*)	22 (40.7%)	19 (35.2%)	
61-70 years (*n*)	26 (48.1%)	25 (46.3%)	
71-80 years (*n*)	2 (3.7%)	4 (7.4%)	
Sex			
Male	24 (44.4%)	24 (44.4%)	
Female	30 (55.6%)	30 (55.6%)	
Hypertension [(*n*) %]	44 (81.5%)	12 (22.2%)	<0.001
Diabetes Mellitus [(*n*) %]	16 (29.6%)	10 (18.5%)	0.177
Smoking [(*n*) %]	17 (31.5%)	18 (33.3%)	0.837
Alcohol [(*n*) %]	13 (24.1%)	10 (18.5%)	0.481
Body Mass Index (kg/m^2)			
Mean±SD	23.56±2.52	22.72±2.15	0.066
Anemia [(*n*) %]	10 (18.5%)	2 (3.7%)	0.028
Dyslipidemia [(*n*) %]			
Total cholesterol (≥200 mg/dL) [(*n*) %]	22 (40.7%)	3 (5.6%)	<0.001
Low density lipoprotein (≥160 mg/dL) [(*n*) %]	10 (18.5%)	3 (5.6%)	0.038
High Density lipoprotein (≤40 mg/dL) [(*n*) %]	11 (20.4%)	2 (3.7%)	0.008
Triglycerides (≥150 mg/dL) [(*n*) %]	18 (33.3%)	2 (3.7%)	<0.001
Vitamin D deficiency (<20 ng/ml) [(*n*) %]	48 (88.9%)	30 (55.6%)	<0.001

Table 2: Distribution of RVO in various seasons

Season	Cases [*n* (%)]	Control [*n* (%)]
Summer	9 (16.7%)	9 (16.7%)
Monsoon	4 (7.4%)	4 (7.4%)
Autumn	16 (29.6%)	16 (29.6%)
Winter	25 (46.3%)	25 (46.3%)

Table 3: Comparison of serum vitamin D levels (ng/ml) in both the groups

Parameter	Cases (mean±SD) ng/ml	Control (mean±SD) ng/ml	*P*
Mean	14.19±5.23	19.42±10.27	0.001
Age			
40-60 years	13.64±5.47	16.92±7.36	0.08
61-80 years	14.70±5.05	21.57±11.96	0.007
Sex			
Male	13.89±4.80	17.76±7.38	0.471
Female	14.43±5.63	20.96±12.31	0.257

non-hypertensive patients in both cases and controls groups and no statistically significant difference was noted [Table 5].

Ten/54 (18.5%) patients had anemia in cases group compared to 2/54 (3.7%) participants with anemia in control group (*P* value = 0.028) [Table 1]. The odds ratio calculated was 4.017 (95% CI = 0.627–26.907), indicating anemia to be associated with RVO disease [Table 4].

Total cholesterol [22/54 (40.7%)], LDL [10/54 (18.5%)], and triglycerides [18/54 (33.3%)] were found to be statistically higher in cases group compared to control group, 3/54 (5.6%), 3/54 (5.6%), and 2/54 (3.7%), respectively [Table 1]. HDL [11/54 (20.4%)] was found to be statistically lower in cases group compared to control group [2/54 (3.7%)] (*P* value = 0.008) [Table 1]. The odds ratio by multivariate logistic regression was calculated to be 6.425 (95% CI = 0.897-46.023) for total cholesterol (≥200 mg/dL), 4.909 (95% CI = 0.736-32.738) for LDL (≥160 mg/dL), and 1.656 (95% CI = 0.172-15.949) for triglycerides (≥150 mg/dL), indicating that higher levels of cholesterol, LDL, and triglycerides are associated with higher risk for RVO [Table 4]. Lower levels of HDL (≤40 mg/dL) are associated with higher risk for RVO [odds ratio 2.353 (95% CI = 0.230-24.033)] [Table 4]. The above indicates that dyslipidemia is a risk factor for RVO disease.

Diabetes mellitus was seen in 16/54 (29.6%) of cases compared to 10/54 (18.5%) of control group participants (*P* value = 0.177). Smoking and alcohol intake were noted in 17/54 (31.5%) and 12/54 (24.1%), respectively, in patients of cases group. In control group, smoking and alcohol intake were noted in 18/54 (33.3%) and 10/54 (18.5%) participants, respectively. Both were not statistically significant [Table 1]. The mean BMI calculated for cases group was 23.56 ± 2.52, and that for the control group was 22.72 ± 2.15 (*P* value = 0.066) [Table 1].

Discussion

RVO is a thromboembolic disease affecting the retinal vasculature. There has been increasing evidence in the literature regarding the role of vitamin D deficiency with an increase in thrombotic episodes.[2–4] Recent studies have demonstrated the association of low vitamin D levels with the development of deep venous thrombosis (DVT).[2–4] Further, Blondon *et al.*[18] found a protective effect of vitamin D supplementation on the risk of unprovoked venous thromboembolism (VTE). Studies in the literature have also highlighted the role of vitamin D in maintaining endothelial function and preventing vascular diseases like HTN, coronary, and cerebrovascular accidents.[5–10] This points towards vitamin D deficiency being a significant risk factor for thrombotic diseases.

The above is supported by evidence from literature that vitamin D through its interaction with receptors on vascular endothelium has a protective role by increasing nitric oxide formation and hence decreasing the oxidative stress on the vascular endothelium.[19,20] Vitamin D has a suppressive effect on vascular smooth muscle cells, which are responsible for vascular calcification, hence having an antiatherogenic role.[21] Vitamin D is also known to have inhibitory effects on renin-angiotensin system, whose hyperactivity is known to cause HTN.[22] Vitamin D modulates immunological responses towards humoral T helper cells 2 (Th2),

Table 4: Multivariate logistic regression to find out significant risk factors of RVO

Variable	Beta coefficient	Standard error	*P*	Odds ratio	Odds ratio Lower bound (95%)	Odds ratio Upper bound (95%)
Anemia	1.413	0.959	0.141	4.107	0.627	26.907
Hypertension	3.007	0.636	<0.0001	20.221	5.812	70.347
Total cholesterol (≥200 mg/dL)	1.860	1.005	0.064	6.425	0.897	46.023
Low density lipoprotein (≥160 mg/dL)	1.591	0.968	0.100	4.909	0.736	32.738
High Density lipoprotein (≤40 mg/dL)	0.856	1.186	0.471	2.353	0.230	24.033
Triglycerides (≥150 mg/dL)	0.505	1.155	0.662	1.656	0.172	15.949
Vitamin D deficiency (<20 ng/ml)	2.357	0.767	0.002	10.558	2.346	47.509

Table 5: Association of Serum vitamin D (ng/mL) with hypertension in study participants

Serum vitamin D (ng/ml)	Hypertensive patients	Non Hypertensive patients	*P*
Cases (Mean±SD)	14.45±5.31	13.07±4.97	0.455*
Controls (Mean±SD)	20.39±6.21	19.15±11.21	0.716*

*Independent *t* test

who have an inhibitory effect on proatherogenic cytokines.[23] It has been proven to be inversely related to type 1 plasminogen activator inhibitor making vitamin D anti-atherogenic.[24] Hence, vitamin D has immunomodulatory and anti-atherogenic roles in our body and its deficiency can predispose to thromboembolic diseases. This has been further supported by results from a recent randomised control trial which investigated the occurrence of major cardiovascular events between adults taking monthly doses of vitamin D supplementation and placebo group over 5 years and found that the rate of major cardiovascular events was lower in the vitamin D supplementation group compared to placebo group.[25]

Our study noted a significant deficiency of serum vitamin D levels in patients of RVO (14.19 ± 5.23 ng/ml) compared to controls (19.42 ± 10.27 ng/ml) (*P* value < 0.001) with an odds ratio of 10.558 (CI = 2.34-47.50). Recently published case-control studies have reported deficiency of vitamin D in 51.4% of CRVO patients compared to 39.3% in control group; an odds ratio of 133.33 for RVO cases versus controls indicates vitamin D deficiency to be strongly associated with RVO and the range of vitamin D in RVO cases (7-25.80 ng/ml) to be significantly less than controls (14.89-33.60 ng/ml).[11–13] The results of our study are in agreement with previous case control studies reporting a positive correlation between vitamin D deficiency and RVO.[11–14] Our study was conducted in patients of North India, whereas previous studies have been done in South India, Sweden, and United States, all reaching similar conclusions.

Recent evidence has come to light that vitamin D can be metabolised locally in the eye. Vitamin D hydroxylases are present in ocular structures like sclera, cornea, ciliary body, and retina, suggesting vitamin D to be an important intraocular mediator in eye diseases.[26,27] Vitamin D receptor (VDR), a nuclear hormone receptor, is expressed in structural elements of the eye, and certain polymorphisms of the VDR gene may lead to the occurrence of eye diseases like diabetic retinopathy and dry eyes.[26,28,29] This has been elucidated by clinical studies documenting the worsening of diabetic retinopathy and dry eyes in cases of vitamin D deficiency.[30,31] In a pioneer study by Uzel *et al.* (2019),[32] they published that vitamin D deficiency causes a decrease in ocular blood flow. This can explain that a decrease in ocular blood flow and loss of anti-atherogenic protection provided by vitamin D can result in thrombo-embolic and vascular occlusive disease, that is, RVO.

In our study, maximum RVO cases (48.1%) were seen in the age group between 61 and 70 years. This can be attributed to decreased dietary intake and reduced synthesis of vitamin D with age.[33] With the increase in age, our skin becomes less efficient at making vitamin D due to a decrease in levels of pro-vitamin D3 in the epidermis. In India, the darker skin has a greater amount of melanin, which absorbs much of the sun's UVB rays before they reach to deeper levels to form vitamin D. Also, the elderly do not come out in the sun and are more homebound, which also affects the vitamin D production. Vitamin D deficiency is known to be as high as 91.2% in this age group of Indian community.[34]

Our study also found a greater number of RVO cases in the winter season, which is in agreement with previous studies.[11] A cold environment causes an increase in platelets, blood viscosity, red blood cells, and fibrinogen (thrombotic agents) and a decrease in antithrombin III (antithrombotic agent).[35–37] Skin exposure to sunlight is decreased due to wearing full sleeves and keeping the body fully covered. A national study in United States identified increased risk of mortality associated with DVT/VTE in the winter months.[38]

Hypertension, dyslipidemia, and anemia are well-established risk factors in RVO, which was also found in the results of our study.[39] DM, BMI, smoking, and alcohol intake did not emerge as risk factors for RVO in our study.

Conclusion

RVO is a sight-threatening disease with poor and highly unpredictable prognosis.[40] It is complicated by macular edema and neovascular glaucoma-threatening vision even after the episode of RVO. Hence, prevention is better than cure. Our study shows a positive association of vitamin D deficiency with RVO and explains the physiological basis of this clinical observation as per literature evidence to date.

Improving the nutritional status of the community for vitamin D micronutrient can help prevent cardiovascular, deep vein thrombosis, and cerebrovascular accidents, which can be life-threatening, and RVO, which can be vision-threatening. Hence, general physicians should aim to counsel all patients on the importance of sunlight exposure and advise oral supplementation of vitamin D in case of deficient patients. Public health measures to include vitamin D micronutrient as a part of food fortification should be implemented to prevent its deficiency. General physicians must include serum vitamin D as a part of battery of tests while assessing the cause of vascular occlusions in any patient. In patients of prior history of vascular occlusions and cardiovascular diseases, oral monthly vitamin D supplementation may be considered as a preventive measure against future vascular occlusions.

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Conflicts of interest

There are no conflicts of interest.

References

1. Song P, Xu Y, Zha M, Zhang Y, Rudan I. Global epidemiology of retinal vein occlusion: A systematic review and meta-analysis of prevalence, incidence, and risk factors. J Glob Health 2019;9:010427.
2. Korkmaz UTK, Ersoy S, Yuksel A, Celik H, Ucaroglu ER, Velioglu Y, *et al.* Association between vitamin D levels and lower-extremity deep vein thrombosis: A case-control study. Sao Paulo Med J Rev Paul Med 2021;139:279–84.
3. Wu WX, He DR. Low Vitamin D Levels Are Associated With the Development of Deep Venous Thromboembolic Events in Patients With Ischemic Stroke. Clin Appl Thromb Off J Int Acad Clin Appl Thromb 2018;24 (9_suppl):69S-75S.
4. Khademvatani K, Seyyed-Mohammadzad MH, Akbari M, Rezaei Y, Eskandari R, Rostamzadeh A. The relationship between vitamin D status and idiopathic lower-extremity deep vein thrombosis. Int J Gen Med 2014;7:303–9.
5. Snijder MB, Lips P, Seidell JC, Visser M, Deeg DJH, Dekker JM, *et al.* Vitamin D status and parathyroid hormone levels in relation to blood pressure: A population-based study in older men and women. J Intern Med 2007;261:558–65.
6. Akin F, Ayça B, Köse N, Duran M, Sari M, Uysal OK, *et al.* Serum vitamin D levels are independently associated with severity of coronary artery disease. J Investig Med Off Publ Am Fed Clin Res 2012 Aug; 60:869–73.
7. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: A double-blind, randomized, placebo-controlled trial. Am J Clin Nutr 2006;83:754–9.
8. Pál É, Ungvári Z, Benyó Z, Várbíró S. Role of vitamin D deficiency in the pathogenesis of cardiovascular and cerebrovascular diseases. Nutrients 2023;15:334.
9. Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD. Vitamin D improves endothelial function in patients with Type 2 diabetes mellitus and low vitamin D levels. Diabet Med J Br Diabet Assoc 2008;25:320–5.
10. Kim DH, Meza CA, Clarke H, Kim JS, Hickner RC. Vitamin D and endothelial function. Nutrients 2020;12:575.
11. Epstein D, Kvanta A, Lindqvist PG. Vitamin D deficiency in patients with central retinal vein occlusion: A case control study. Curr Eye Res 2017;42:448–51.
12. Oli A, Joshi D. Serum vitamin D levels in Indian patients with retinal venous occlusions. Saudi J Ophthalmol Off J Saudi Ophthalmol Soc 2017;31:76–9.
13. Muttar AAZ, Hamiedd F Majied. Association between low serum vitamin D level and retinal venous occlusion at lbn- Alhaitham eye teaching hospital. AL-QADISIYAH Med J 2022;18:1–9.
14. Kandambeth V, Nagrale P, Daigavane S. Estimation of vitamin D levels in patients with retinal vein occlusions and a comparison with age-matched control groups. Cureus 2023;15:e38909.
15. National Health and Nutrition Examination Survey. Anthropometry procedure manual. 2007. Available from: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/manual_an.pdf. [Last accessed on 2024 Mar 24].
16. Holick MF. Vitamin D deficiency. N Engl J Med 2007 Jul 19;357:266–81.
17. Climate of India. In: Wikipedia. 2024. Available from: https://en.wikipedia.org/w/index.php?title=Climate_of_India& oldid=1213256476. [Last accessed on 2024 Mar 24].
18. Blondon M, Rodabough RJ, Budrys N, Johnson KC, Berger JS, Shikany JM, *et al.* The effect of calcium plus vitamin D supplementation on the risk of venous thromboembolism. From the Women's Health Initiative Randomized Controlled Trial. Thromb Haemost 2015;113:999–1009.
19. Molinari C, Uberti F, Grossini E, Vacca G, Carda S, Invernizzi M, *et al.* 1α,25-dihydroxycholecalciferol induces nitric oxide production in cultured endothelial cells. Cell Physiol Biochem Int J Exp Cell Physiol Biochem Pharmacol 2011;27:661–8.
20. Polidoro L, Properzi G, Marampon F, Gravina GL, Festuccia C, Di Cesare E, *et al.* Vitamin D protects human endothelial cells from H□O□ oxidant injury through the Mek/Erk-Sirt1 axis activation. J Cardiovasc Transl Res 2013;6:221–31.
21. Aoshima Y, Mizobuchi M, Ogata H, Kumata C, Nakazawa A, Kondo F, *et al.* Vitamin D receptor activators inhibit vascular smooth muscle cell mineralization induced by phosphate and TNF-α. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc-Eur Ren Assoc 2012;27:1800–6.
22. Li YC, Qiao G, Uskokovic M, Xiang W, Zheng W, Kong J. Vitamin D: A negative endocrine regulator of the renin-angiotensin system and blood pressure. J Steroid Biochem Mol Biol 2004 May; 89–90:387–92.
23. Hewison M. Vitamin D and the immune system: New perspectives on an old theme. Rheum Dis Clin North Am 2012;38:125–39.
24. Wu-Wong JR, Nakane M, Ma J. Vitamin D analogs modulate the expression of plasminogen activator inhibitor-1, thrombospondin-1 and thrombomodulin in human aortic smooth muscle cells. J Vasc Res 2007;44:11–8.
25. Thompson B, Waterhouse M, English DR, McLeod DS, Armstrong BK, Baxter C, *et al.* Vitamin D supplementation and major cardiovascular events: D-Health randomised

controlled trial. BMJ 2023;381:e075230.

26. 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.
27. Rullo J, Pennimpede T, Mehraban Far P, Strube YN, Irrcher I, Urton T, *et al.* Intraocular calcidiol: Uncovering a role for vitamin D in the eye. J Steroid Biochem Mol Biol 2020;197:105536.
28. Yin Z, Pintea V, Lin Y, Hammock BD, Watsky MA. Vitamin D enhances corneal epithelial barrier function. Invest Ophthalmol Vis Sci 2011;52:7359–64.
29. Hong YJ, Kang ES, Ji MJ, Choi HJ, Oh T, Koong SS, *et al.* Association between Bsm1 polymorphism in vitamin D receptor gene and diabetic retinopathy of type 2 diabetes in Korean population. Endocrinol Metab Seoul Korea 2015;30:469–74.
30. Luo BA, Gao F, Qin LL. The association between vitamin D deficiency and diabetic retinopathy in type 2 diabetes: A meta-analysis of observational studies. Nutrients 2017;9:307.
31. Liu J, Dong Y, Wang Y. Vitamin D deficiency is associated with dry eye syndrome: A systematic review and meta-analysis. Acta Ophthalmol (Copenh) 2020;98:749–54.
32. Uzel AT, Ünal O, İyidoğan D, Ürer ES, Uğurlu N, Uzel MM. Effect of vitamin D deficiency on ocular blood flow. Ann Clin Anal Med 2022;13:1158-61.
33. Gallagher JC. Vitamin D and aging. Endocrinol Metab Clin North Am 2013;42:319–32.
34. Marwaha RK, Tandon N, Garg MK, Kanwar R, Narang A, Sastry A, *et al.* Vitamin D status in healthy Indians aged 50 years and above. J Assoc Physicians India 2011;59:706–9.
35. Neild PJ, Syndercombe-Court D, Keatinge WR, Donaldson GC, Mattock M, Caunce M. Cold-induced increases in erythrocyte count, plasma cholesterol and plasma fibrinogen of elderly people without a comparable rise in protein C or factor X. Clin Sci Lond Engl 1979 1994;86:43–8.
36. Keatinge WR, Coleshaw SR, Cotter F, Mattock M, Murphy M, Chelliah R. Increases in platelet and red cell counts, blood viscosity, and arterial pressure during mild surface cooling: Factors in mortality from coronary and cerebral thrombosis in winter. Br Med J Clin Res Ed 1984;289:1405–8.
37. Bull GM, Brozovic M, Chakrabarti R, Meade TW, Morton J, North WR, *et al.* Relationship of air temperature to various chemical, haematological, and haemostatic variables. J Clin Pathol 1979;32:16–20.
38. Styler M, Singhal S, Halkidis K, Patel P, Ward KM, Jain M. The impact of winter months on Venous Thromboembolism (VTE) patients: A retrospective analysis of hospital outcomes in the United States. Cureus 2022;14:e29091.
39. Kolar P. Risk factors for central and branch retinal vein occlusion: A meta-analysis of published clinical data. J Ophthalmol 2014;2014:724780.
40. Glacet-Bernard A, Coscas G, Chabanel A, Zourdani A, Lelong F, Samama MM. Prognostic factors for retinal vein occlusion: Prospective study of 175 cases. Ophthalmology 1996;103:551–60.