Association between low serum vitamin D level and retinal venous occlusion at lbn-Alhaitham eye teaching hospital

Afrah Abdul Zahraa Muttar*, Furkaan majied Hamiedd**

*** F.I.C.M.S (Ophth.)**
****M.B.CH.B. F.I.C.M.S (Ophth.) Professor ,College of medicine/Al-Qadisiyah University**

Abstract

Background: Retinal vein occlusion is the second most common cause of sudden vision loss from retinal vascular diseases, following diabetic retinopathy. The role of vitamin D in maintaining the vascular system is now being increasingly understood and the effect of Vitamin D deficiency on vascular endothelium could possibly have some role to play in the causation of retinal vein occlusion.

Objective:To estimate serum vitamin D3 (25 OH D) level in patients of retinal vein occlusion and compare it with age and gender -matched controls.

Subject and methods: This study is a hospital-based, case-control study conducted between October 2017 and February 2018 and included 35 cases of retinal venous occlusion (14 cases of branch retinal vein occlusion and 21 cases of central retinal vein occlusion, no cases of hemiretinal venous occlusion) with onset less than three months were enrolled. These cases were compared with 35 age and gender matched attendants of patients as controls, as they had comparable dietary and socioeconomic condition. Serum vitamin D3 (25 OH D) was done for cases and control group. Student's t test was used to assess the significance of differences in mean vitamin D levels, while chi square test was used to assess the significance of association and comparison of frequencies in categorical variables. Level of significance of ≤ 0.05 considered as cutoff for significant difference or association.

Results*:* the mean serum vitamin D level was significantly lower in retinal vein occlusion group than controls, (14.21 ± 5.19) ng/ml and (22.70 ± 4.43) ng/ml, respectively, on the other hand, vitamin D level in these cases ranged (7 – 25.80) ng/ml which was also lower than that in controls (range: 14.89 – 33.60)ng/ml, the difference in mean vitamin D level between groups was highly significant (**P< 0.001**).There was no statistical difference in serum vitamin D between branch and central retinal vein occlusion (P. value 0.34).

Conclusion*:* Vitamin D deficiency was more common in patients with retinal vein occlusion in realtion to healthy population.

Introduction

Retinal vein occlusion (RVO) is an important etiology of visual loss among older adults throughout the world [(1)].

Classification: The anatomic division of RVO is derived from the fundoscopic appearance of the eye and includes three main groups depending on the location of venous occlusion: branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), and hemi retinal vein occlusion (HRVO).[(2)]

Further classification are related to the amount of retinal capillary non perfusion observed on fluorescein angiography [(3)]

Pathogenesis: Retinal vein thrombosis is strongly related to age-related local and systemic factors where degenerative changes of the vessel wall, venous stasis, and blood hypercoagulability may increase the risk of thrombosis (Virchow´s triad) [(4)].

Etiology and Risk factors: The most recognized risk factors for RVO are age and systemic vascular disorders. In over half of the cases, the age of onset is over 65 years. However, patients under 45 can also develop an RVO [5].

These several risk factors for retinal venous occlusion are well known and discussed in the literature. Other non-classical factors are:

1.Temperature: Both reduced indoor and outdoor temperature as recorded during winter have been shown to significantly increase blood pressure [6].

2.Physical activity:[7].

3.Vitamin D deficiency [8].

Vitamin D: Vitamin D (known as the sunlight hormone) has long been known to regulate serum calcium and phosphate metabolism and promoting bone mineralization, numerous publications have shown that vitamin D may also have an impact on several other physiological functions and deficiency has been associated with rickets , osteomalacia, CVD, autoimmune diseases, type 2 diabetes mellitus, cancer and infectious diseases, 3-4 fold increase risk for developing preeclampsia, and venous thromboembolism [9].

Vitamin D and retinal venous occlusion:

The mechanism for how vitamin D can affect vascular disease outcomes has not yet completely elucidated. The proposed mechanisms are:

i. Inhibition of the renin-angiotensin-system:[10].

ii. Stimulate endothelial and vascular function:[8].

iii. Levels of 25(OH)D were found to be inversely related to type 1 plasminogen activator inhibitor [11]

Aim of the study

To identify serum vitamin D3 (25 OH D) level in patients of retinal vein occlusion and compare it with age and gender -matched control.

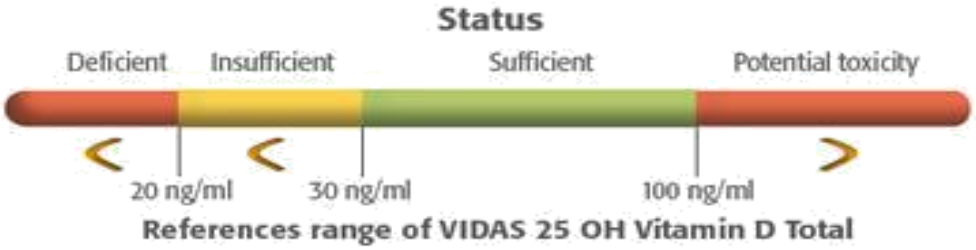
Subjects and methods

Study design: This study is a hospital-based, case-control study taken between October 2017 and February 2018.

Subjects: In this study thirty-five patients of retinal venous occlusion (14 cases of BRVO and 21 cases of CRVO, but no cases of hemiretinal venous occlusion were identified) with onset less than three months were included. Those patients were taken on the basis of clinical history, examination, and investigations, irrespective of sex and socioeconomic status.

These cases were compared with thirty-five age and gender matched attendants of patients as controls, as they had comparable dietary and socioeconomic condition. The selected patients sent to ophthalmic evaluation consisting of visual assessment, pupillary reaction, fundus photo, Fluorescein angiography and Optical Coherence Tomography. Medical history of diabetes mellitus (DM), hypertension (HTN) and smoking was included. The patients also underwent systemic evaluation by physician.

After fasting for 12 hours, five ml of blood sample was aspirated from each patient. The sample was centrifuged and analyzed using VIDAS® 25 OH Vitamin D Total (is an automated quantitative test for the determination of 25-hydroxyvitamin D3 Total in human serum or plasma using the ELFA (Enzyme Linked Fluorescent Assay) technique, very well correlated to the Liquid Chromatography-Mass Spectrometry/Mass Spectrometry (LC-MS/MS) reference method).



Statistical analysis

Data of this study participants were analyzed using the statistical package for social sciences (SPSS), software for windows, version 24. Student's t test was taken to identify the significance of differences in mean vitamin D levels, while chi square test (X2) was used to assess the significance of relationship and comparison of frequencies in categorical variables. Level of significance of ≤ 0.05 considered as cutoff for significant difference or association.

Ethical issues:

Informed verbal consents was taken from the patients and controls.

Results

Table 1. Demographic characteristics of the studied group

Variable		RVO patients (n = 35)		Controls (n = 35)		Odd ratio	5%Confidence	*P. value*
		No.	%	No.	%			
Age (year)	**<50**	**13**	**37.14**	**9**	**25.71**	**1.707**	**0.614-4.744**	**0.30**
	≥50	**22**	**62.86**	**26**	**74.28**			
Gender	**Male**	**20**	**57.14**	**17**	**48.57**	**1.412**	**0.550-3.622**	**0.47**
	Female	**15**	**42.85**	**18**	**51.42**			
Residency	**Urban**	**21**	**60.00**	**19**	**54.28**	**1.263**	**0.489-3.261**	**0.62**
	Rural	**14**	**40.00**	**16**	**45.14**			
Risk factor	**HT**	**17**	**48.57**	**10**	**28.57**	**3.778**	**1.247-11.447**	**0.059**
	DM	**5**	**14.28**	**2**	**5.71**	**5.556**	**0.901-34.249**	
	Both	**4**	**11.42**	**3**	**8.57**	**2.963**	**0.546-16.075**	
	None	**9**	**25.71**	**20**	**57.14**	**1**	**------**	
Smoking habit	**Smokers**	**9**	**25.71**	**10**	**28.57**	**0.865**	**0.301-2.485**	**0.78**
	Nonsmokers	26	74.28	25	71.42			

s it shown in (**Table 2**), the mean serum vitamin D level was significantly lower in RVO group than controls, (14.21 ± 5.19) ng/ml and (22.70 ± 4.43) ng/ml, respectively, on the other hand, vitamin D level in RVO group ranged (7 – 25.80) ng/ml which was also lower than that in

controls (range: 14.89 – 33.60), (**Figure 1**), the difference in mean vitamin D level between groups was highly significant (**P< 0.001**).

Table 2. Comparison of Serum Vitamin D level of RVO patients and controls

Statistics	Serum Vitamin D level (ng/ml)		
	RVO patient (n = 35)	Control (n = 35)	5% confidence interval
Mean ± SD*	14.21 ± 5.19	22.70 ± 4.43	1.2135-7.3212
Minimum	7.00	14.89	
Maximum	25.80	33.60	
P value (comparison of means) = < 0.001(significant difference)			

**SD: standard deviation*

Figure 1. Graphical comparison of mean Serum vitamin D level between the studied groups

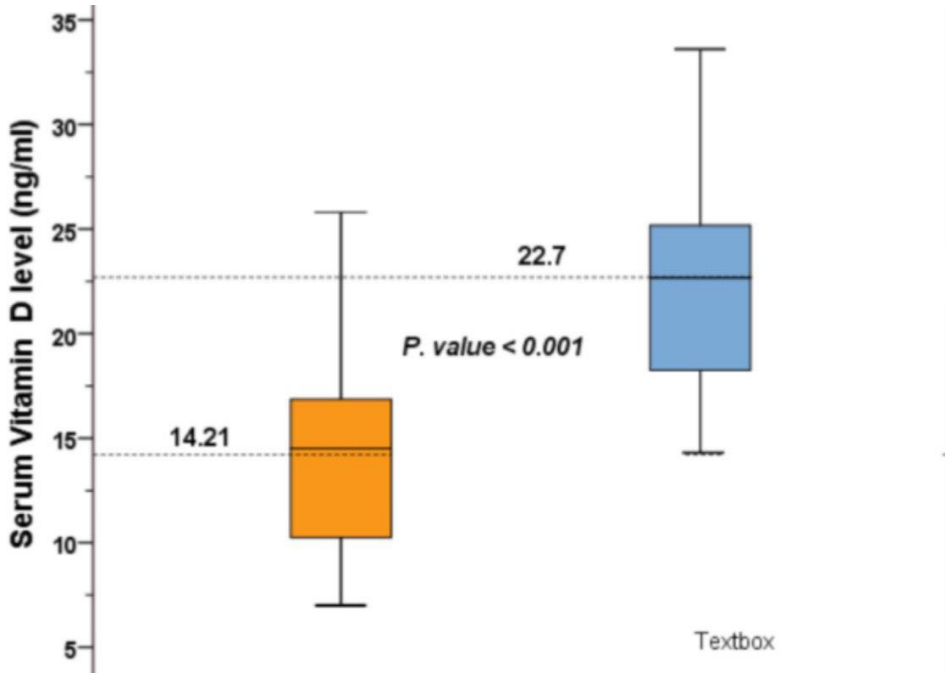


Table 3. Distribution of serum vitamin D level of RVO patients and controls according to reference values

Vitamin D level	RVO patient (n =35)		Control (n = 35)		Odd ratio	5% confidence	P value
	No.	%	No.	%			
Deficiency	29	82.85	8	22.85	0.216	0.117-0.399	0.003
Insufficiency	6	17.14	24	68.57	0.800	0.669-0.957	0.392
Sufficient	0	0.00	3	8.57	1	-----	1

Table 4. comparison between serum vitamin D levels and demographic characteristics of RVO patients (N = 35)

		Serum Vitamin D level				P value		
Variable		Deficiency (n = 29)		Insufficiency (n = 6)			Odds ratio	Confidence 5%
		no.	%	no.	%			
Age (year)	<50	11	84.62	2	15.38	0.80	1.222	0.91-7.818
	≥50	18	81.82	4	18.18			
Gender	Male	17	85.00	3	15.00	0.94	1.172	0.243-8.256
	Female	12	80.00	3	20.00			
Residency	Urban	15	71.43	6	28.57	0.082	0.517	0.364-0.735
	Rural	14	1.00	0	0.00			

Table 5. comparison between serum vitamin D levels and demographic characteristics of RVO patients (N = 35)

Variable		Serum Vitamin D level				P value	Odds ratio	Confidence 5%
		Deficiency (n = 29)		Insufficiency (n = 6)				
		No.	%	No.	%			
Risk factor	HT	14	82.35	3	17.65	0.660	0.583	0.052-6.587
	DM	4	80.0	1	20.0	0.649	0.500	0.024-10.251
	Both	4	100.0	0	0.00	0.488	0.667	0.447-0.995
	None	8	88.89	1	11.11	1	1	---
Smoking habit	Smokers	22	84.62	4	15.38	0.64	1.571	0.235-10.491
	Nonsmokers	7	77.78	2	22.22			

Table 6. Comparison of mean vitamin D level according to the type of RVO

Type	No.	%	Vitamin D Mean ± SD	5% Confidence interval
CRVO	21	60.0	13.25 ± 5.01	-2.5725-4.8266
BRVO	14	40.0	15.25 ± 5.47	
P. value	35	0.09	0.34	

SD: standard deviation

Discussion

Retinal vein occlusion (RVO) is a significant health problem seen in practice of ophthalmology. If this closure is not resolved, a number of complications can occur manifested in reduced retinal oxygenation and leads to excessive expression of the protein vascular endothelial growth factor (VEGF) [12],[13].

However, the relationship between vitamin D deficiency and RVO is not well established, therefore, the current study tried to assess the relationship between vitamin D deficiency and RVO, hence, 35 patients with RVO were compared to 35 controls without RVO and their serum vitamin D level was assessed in the current case control study among group of Iraqi patients. Patients and controls were compared regarding their age, gender and residence, and no statistically significant differences had been reported between both groups in these variables, (P>0.05), this comparisons in these variables were performed to exclude any possible confounding effect on the findings, where vitamin d level could potentially affected by age, gender or residence, this indicated a good designing of he case control study [15].

however, it was inapplicable to make complete matching between both groups. Similarly, risk factor distribution was insignificantly different between both groups, (P>0.05) and also no significant difference regarding smoking, (P>0.05), the insignificant difference in smoking status was also to controlling its confounding effect on vitamin D level , the designing of case control studies requires special precaution by the researcher and to be aware about the confounding effect of these variables, where previous studies suggested an inter-correlation between RVO and these variables and also an inter-correlation between vitamin D

levels and these variables or risk factors such as diabetes and hypertension (16),(17), (18), (19)

The lower levels of vitamin D in RVO patients compared to control reported in the current study indicated a significant correlation between lower vitamin D levels and RVO, and vitamin D deficiency could be a risk factor for RVO, these findings were also reported in previous studies in recent past; In a recent Indian study published in 2017 , Oli and Joshi [14], studied 40 patients above the age 18 with RVO and compared them to 40 age-matched controls, they found that the mean vitamin D level of RVO patients was (13.68 ± 4.58) ng/ml (range 5.5 – 24.80) which was significantly lower than that among controls, 23.03 ± 2.89 (range: 18.4 – 30.1) ng/ml, these levels were close to that reported among the Iraqi patients and contols of the current study, furthermore, Oli and Joshi [14],when compare vitamin D levels as categories, found that 95% of the RVO patients had deficient vitamin D level, which was higher than that reported in the present study, and only 8% of controls with vitamin d deficiency which was lower than that reported among controls.

An earlier study was conducted by the same authors Oli and Joshi (2014)

suggested that vitamin D level is a risk factor of RVO and they based their study on the fact that RVO and vascular diseases share common risk factors,

However, the insignificant differences reported in the current study could be attributed firstly to the small sample size, on the other hand, in this study, neither risk factors nor smoking was obviously seen with vitamin d deficiency

Furthermore, this study assessed vitamin D levels across the types of occlusions, and conclude that there is no statistically significant differences in vitamin D levels across both types of occlusions CRvO and BRVO.

The current study is not free of limitations; in fact the restriction in time and financial resources contributes in lower sample size, other limitation is that vitamin d concentration was not assessed at the time of onset of RVO so the onset of vitamin D

deficiency couldn't be proved to be started before RVO, nonetheless further studies, particularly clinical trials with larger sample size and longer duration could rule out these limitations, and the current study focus the light on the possible association between vitamin D deficiency and RVO. differences in vitamin D levels across both types of occlusions CRvO and BRVO.

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Conclusions

Vitamin D deficiency was more frequent in patients with RVO compared to healthy population.

Vitamin D levels of patients with retinal vein occlusion were not affected by their age, gender, residency, smoking or the presence of risk factors.

Frequency of Vitamin D deficiency was not much different across the type of occlusion.

Recommendations:

1.Assessment of vitamin D level in patients with retinal vein occlusion.

2.Serum Vitamin D could be used as a promising marker of RVO in addition to the clinical and traditional test

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