



Estimating the Vitamin-D Levels in Patients with Retinal Vein Occlusions: A Case Control Study

Varsha Kandambeth^{a*#} and Pradeep Sune^{a≡}

^a Department of Ophthalmology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Deemed to be University, Wardha, India.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Study Protocol

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ABSTRACT

Background: Retinal vein occlusion in diabetic retinopathy resulting in visual impairment and complete vision loss is well-known especially in older population. Ischemic occlusion of retinal vein can cause macular edema, macular ischemia and neovascularization which might end up in complete vision loss. Role of Vitamin D in maintaining vasculature and function of endothelium is evident from a number of studies. This study aims to estimate vitamin D levels in individuals with retinal vein occlusions.

Methodology: This will be a hospital based case control study conducted in Ophthalmology department of AVBRH, Wardha. About 70 consecutive patients will be enrolled and assigned to Case and Control groups of 35 each. Vitamin D levels will be estimated in all 70 patients. Including best corrected visual acuity (snellens chart), slit lamp inspection, intraocular pressure (IOP) measurement (Applanation tonometer) and fundoscopy (slit lamp biomicroscopy with 90 D) will be performed on all patients. Data will be collected, tabulated and compiled. Statistical analysis will be done by using unpaired student t test and Chi square test.

Expected results: Expected findings include deficient vitamin D levels in patients with retinal vein occlusion.

Conclusion: Retinal vein Occlusions are a leading reason for vision impairment which is preventable by timely treatment with Vitamin D.

[#] Post Graduate Resident,

[≡] Professor,

^{*}Corresponding author: E-mail: varsharey@gmail.com;

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1. INTRODUCTION

Retinal vein occlusion is a popular and common source of disease affecting the retinal vasculature succeeding diabetic retinopathy and is a usual reason for visual impairment and complete vision loss worldwide [1]. Retinal vein occlusions can be categorized into, occlusion of hemi central retinal vein (HCRVO), branch retinal vein occlusion (BRVO) and occlusion of central retinal vein (CRVO) based where the occlusion is. Risk factors associated with retinal vein Occlusions like diabetes, raised blood pressure, hyperlipidemia, and prothrombotic states are alike to other vascular diseases like cardio and cerebrovascular disorders [2,3]. Occlusion of branch retinal vein (BRVO) is associated with arteriosclerosis of a branch retinal arteriole which compresses at A-V crossings which can be precipitated due to common sheath of adventitia. This can result in secondary changes like loss of endothelial cells, turbulent flow and formation of thrombus. Occlusion of central retinal vein occurs due to the compression of vessels at lamina cribosa which can be exaggerated by sharing the same sheath at A-V crossings which is behind the lamina cribosa because of atherosclerotic process. The symptoms and vision are also based on the anatomical location of the occlusion, for example if there is macular involvement patient may present with a rapid painless loss of vision and metamorphopsia. Peripheral occlusions can be asymptomatic.

Retinal vein Occlusions are categorized into ischemic retinal vein Occlusions and non ischemic retinal vein Occlusions. This classification is clinically assessed in view of the extent of retinal capillary ischemia on fundus fluorescein angiography. Ischemic type is severe and can cause macular edema, macular ischemia and neovascularization which might end up in complete vision loss [4,5].

History should concentrate on the timing, severity, vision loss, trauma involvement or absence, unilateral versus bilateral symptoms.

Asking about risk factors is also important. Occlusion of the branch retinal vein (BRVO) may be asymptomatic and incidentally observed on fundoscopic inspection, or patients may complain of relative scotoma or blurred vision areas, progressively deteriorating over hours or days.

Central retinal vein occlusion (CRVO) patients are usually symptomatic, typically presenting with sudden painless loss of monocular vision or thick central scotoma. In certain cases, with occasional periods of blurred vision, this loss of vision is subtle in character. It may be abrupt and dramatic in some situations. In cases of ischemic CRVO, visual acuity is the vital sign that normally displays ipsilateral relative afferent pupillary defect (RAPD). In each case of suspected retinal vein occlusion intraocular pressure should be tested.

Retinal vein occlusion is basically a blockage at the region that blocks the retinal portion of venous circulation. With blockage, pressure builds up in the capillaries causing fluid and blood to hemorrhage and spill. This may contribute to the leakage causing macular edema near the macula. Macular ischemia occurs when leakage and nonperfusion are manifested by these capillaries, which deliver oxygen to the retina. Neovascularization, the growth of new irregular blood vessels, then occurs, which may lead to neovascular glaucoma, vitreous hemorrhage, and retinal detachment in late or extreme cases. Macular edema, retinal hemorrhage, macular ischemia, and neovascular glaucoma result in visual morbidity and blindness in RVO. Intraluminal thrombus formation is associated with venous stasis, endothelial damage, and hypercoagulability of the Virchow triad in Retinal vein occlusion. In case of suspected RVO, intraocular pressure should be tested. In the initial acute presentation or prior to neovascularization, IOP is usually common. Funduscopy imaging in RVO is diagnostic, as retinal hemorrhage, edema, and dilated veins are seen. The retinal hemorrhage is distributed and diffuse in patients with CRVO or hemiretinal vein occlusion (HRVO), presenting the classic "blood and thunder" fundus (or hemi-fundus).

There is no proper cure for retinal vein Occlusions but treatments are available to treat the complications and prevent further progression. Any macular edema or neovascularization can be treated by intravitreal anti VEGF injections [6,7]. Laser treatments are also widely practiced in case of retinal vein Occlusions. Studies conducted regarding treatment options for central retinal vein Occlusions show positive results with the use of pan retinal photocoagulation in events which

cause neovascularization of iris. Branched retinal vein Occlusions can use grid photocoagulation to the edematous area [8,9,10] .Since there is no cure for retinal vein Occlusions and due to limited treatment options controlling the risk factors is most important.

Vitamin D is one of the fat soluble vitamins, obtained from either food sources or by transformation of 7-dehydrocholesterol available in subcutaneous fat to pro-vitamin D in the presence of UV rays. Since sunlight is essential for this conversion vitamin d is also called as sunlight hormone.It is then hydroxylated to 25 (OH) vitamin D and 1,25 (OH) vitamin D subsequently in liver and kidneys respectively.Vitamin D is involved in the calcium metabolism of our body and is essential for bone growth and prevents tetany associated with hypocalcemia.Vitamin d also helps in reduction of inflammation, glucose metabolism, immune and neuromuscular function and cell growth [11,12,13]. Vitamin D is often considered to be involved in the maintenance of the vascular system and the same has been shown in several studies.

Deficiency of vitamin D leads to a condition called rickets in children, which results in impaired bone growth, muscle weakness and pain in the muscles. However in adults it causes severe fatigue, muscle pain and cramps, bone pain and even depression or mood changes. Deficient vitamin D levels are associated with injury to endothelium and risk factors associated with cardiovascular disorders like hypertension , diabetes, obesity etc . Several studies in the past have pointed out in individuals with retinal vein Occlusions there are higher chances of developing cardiovascular disorders compared to the ones without retinal vein Occlusions [14]. Studies have been conducted in the-past on type 2 diabetic and ischemic heart disease patients regarding the influence of vitamin D on vascular endothelium and how vitamin D supplementation improves endothelial function which have yielded positive results [15,16].

Based on the fact that the risk factors for RVO and other vascular disorders are similar with common pathogenesis of atherosclerosis and there is improvement in vascular endothelial function after vitamin d supplements, we assume that vitamin d could have some influence in the causation of retinal vein Occlusions.

Very few studies are conducted in central India regarding the correlation of retinal vein occlusion

and Vitamin D deficiency, hence we are conducting this study on the hypothesis that there is deficient vitamin D levels in individuals with retinal vein occlusion.

2. MATERIALS AND METHODS

2.1 Research Design

Hospital based prospective case control study

2.2 Settings

All the procedures will be conducted at the department of Ophthalmology, AVBRH, Sawangi under standard conditions by a single surgeon.

2.3 Duration of Study

2 years from September 2020 to September 2022

2.4 Participants

All patients above the age of 18 years with Retinal vein occlusion coming to Ophthalmology OPD and controls in the same age group at AVBRH will be selected for study after considering inclusion and exclusion criteria:

2.5 Inclusion Criteria

Individuals diagnosed with central retinal vein occlusion or branched retinal vein occlusion will be selected for the study

2.6 Exclusion Criteria

- 1) Patients on vitamin D supplementation
- 2) Patients on therapeutic diets
- 3) Patients with kidney, liver, dermatological diseases
- 4) Patients who are chronically habituated to alcohol will be excluded from our study.

2.7 Sampling Procedure

Using sample size formula with desired error of margin

$$n = \frac{Z^2 \alpha/2 * P*(1-P)}{d^2}$$

Where

Z $\alpha/2$ is the level of significance at 5 %

le: 95 % confidence interval =1.96

P=Prevalence of Retinal vein occlusion patients with vitamin D deficiency

d=Desired error of margin=0.8%=0.008

$$n = \frac{1.96^2 \times 0.008 \times (1 - 0.008)}{0.03^2}$$

=33.87

=35 patients needed in the study

Sample size:

- 1) In this case control hospital based study, total 70 consecutive SUBJECTS will be registered after fulfilling inclusion and exclusion criteria .
- 2) Out of which 35 subjects diagnosed of retinal vein occlusion will be taken as cases. 35 subjects who are diagnosed free from retinal vein occlusion in the same age group as cases are taken as controls.

2.8 Data Collection Tools and Process

All patients will be made fully aware of the details of the procedure. The patients fulfilling the inclusion criteria will be sequentially recruited for the study.

2.8.1 Tests

Including best corrected visual acuity (snellens chart), slit lamp inspection, intraocular pressure (IOP) measurement (Applanation tonometer) and funduscopy (slit lamp biomicroscopy with 90 D) will be performed on all patients considering inclusion and exclusion criteria. Clinical history and detailed ophthalmic examination will be taken .

With confirmation from medical reports, the related history of diabetes mellitus (DM), hypertension (HTN), angina (CAD) and stroke (CVA) will be adopted.

Cases will also be subjected to other investigations such as complete blood count(CBC), blood sugar levels (fasting and post prandial), urea, creatinine, electrolytes, thyroid function tests ,lipid profile, erythrocytes sedimentation rate (ESR) and ECG.

Some additional tests such as (a) cases with less than 50 years of age (b) bilateral cases (c) patients with family history suggestive of thrombosis (d) Cases with previous history of thrombosis(e)cases inconclusive after common

investigations like chest X-ray, C-reactive protein(CRP), plasma homocysteine levels, thrombophilia screen, autoantibodies like rheumatoid factor and ANCA, Serum angiotensin converting enzyme (ACE)etc.

2.9 General Examination

Includes vitals ,any pallor, icterus, edema etc. Higher mental functions may also be noted.

2.10 Ocular Examination

This is a prospective study of 70consecutive patients{Randomly Selected from eye OPD} assigned to undergo funduscopy (slit lamp biomicroscopy). Study will be done for a period of two years at AVBRH hospital.

12hrs fasting the blood sample will be acquired from the subjects and vitamin d levels will be assessed by separating the serum and freezing at minus 20 celcius. Then tandem mass spectrometry is carried out to find the total vitamin d levels.70 subjects in total will be included to analyze their vitamin D levels.

Fundus photographs will be taken on Retinal camera TOPCON -TRC-50EX (frequency Q.50/60Hz) as documentation .

2.11 Statistical Analysis

Statistical analysis will be done by using unpaired student t test and Chi square test , and values are considered significant when $p < 0.005$.

2.12 Variables

Retinal vein-occlusions and Vitamin D levels

3. DISCUSSION AND CONCLUSION

Based on the studies available to us we expect to see a statistically significant relation between retinal vein occlusions and vitamin D levels. We also expect to see deficient or at least insufficient levels of vitamin d in subjects with retinal vein occlusions and to be aware of the bit part of vitamin D in vasculature of human eye in these individuals .This study will also help us to understand the association of hypertension, cerebro-vascular accidents and coronary heart disorders with Vitamin D deficiency. There are many studies that prove that low vitamin d levels could be associated with cardiovascular diseases.

Taking cue from those studies vitamin d levels of less than 20 ng/ml is considered deficient and levels ranging from 20 to 30 ng/ml is considered insufficient [17,18]. Deficient vitamin d may be due to lack of dietary intake , less exposure to sunlight , always wearing cloths that fully cover a person and other systemic disorders affecting liver ,kidney etc [19,20,21]. Studies have been conducted in the-past on type 2 diabetic and ischemic heart disease patients regarding the influence of vitamin d on vascular endothelium and how vitamin d supplementation improves endothelial function [22-27]. Retinal vein occlusion is the second most common source of vascular visual impairment in the country .But there is scarcity of literature published on Vitamin D levels in subjects with retinal vein occlusions. Set up of this correlation give us feasible suggestions for prophylaxis or treatment of retinal vein occlusions. Vitamin D deficiency correction may also help in predicting the risk of cardiovascular diseases since there are a lot of common risks associated with them [28-35].

LIMITATIONS

Sample size is small.

- Vitamin D levels might vary depending on the patients fasting status
- Vitamin D may not be assessed at initial stages of the disease.
- Larger studies are required to confirm these results.
- Community based studies are required.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

The patients will be selected after giving written consent in the local language

ETHICAL APPROVAL

The research will be performed in accordance with the principles of Helsinki Declaration and will

be accepted by the DMIMS Institutional Ethical Committee (IEC).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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