



## ASSOCIATION BETWEEN SERUM 25-OH VITAMIN D LEVELS AND SEVERITY OF POAG.

### Ophthalmology

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### ABSTRACT

**Purpose-** To study the association of Serum 25-OH Vitamin D levels in patients of primary open angle glaucoma. **Methods:** 92 subjects aged between 40-70 years, participated in this hospital-based case control study. All glaucomatous (n=46) and non glaucomatous (n=46) patients underwent a comprehensive ophthalmic examination, including intraocular pressure, Oct, Humphreys visual field analysis after taking consent and ethical clearance. Classification of glaucomatous patients was done into early, moderate and advanced based on visual field damage. A Fasting Blood samples were used to analyze for 25-OH Vitamin D levels, using Vitros immunoassay analyzer. **Results.** Out of 46 POAG cases, 19 early grade patients had a visual field mean deviation better than -6 dB, 16 moderate grade had visual field between -12 and <-6 and 11 advanced glaucomatous patients had mean damage worse than -12 dB. The mean 25-OH Vitamin D level in POAG patients was  $19.70 \pm 1.10$  and the mean for age-matched controls was  $24.90 \pm 4.17$ , which was statistically significant. ( $p < 0.001$ ). A significant difference was observed between vitamin D levels of early grade ( $24.26 \pm 4.47$ ) and advanced grade ( $17.85 \pm 1.85$ ) POAG patients. **Conclusions:** In this study, lower serum 25-OH Vitamin D levels were found in advanced glaucoma compared to moderate and early glaucoma. There was an association between a decrease in vitamin D levels with increasing grades of glaucoma, indicating that Vitamin D has a neuroprotective role on the optic nerve.

### KEYWORDS

25-Hydroxy Vitamin-D3; Intraocular Pressure; VF (Visual Field)

### INTRODUCTION

Glaucoma is a major public health problem, being the leading cause of irreversible visual impairment worldwide.<sup>[1]</sup> It is a complex, multifactorial, progressive optic neuropathy resulting in irreversible visual impairment.<sup>[2]</sup> Glaucoma affected 64.3 million people in 2013, which will be increased to 76.0 million in 2040 and further to 111.8 million in 2040.<sup>[3]</sup> Primary open-angle glaucoma (POAG) is the most common type of glaucoma accounting for three-quarters (74%) of all glaucoma cases.<sup>[4]</sup>

POAG is a progressive optic neuropathy associated with visual field deterioration and ganglion cells loss in eyes with gonioscopically open angles, with or without elevated intraocular pressure (IOP).<sup>[5]</sup> A recent review estimated the global number of POAG cases in 2013 at 44 million, rising to 53 million by 2020 due to population aging.<sup>[6]</sup> The main risk factors for both development and progression of glaucoma are older age, an intraocular pressure too high in relation to the pressure sensitivity of the optic nerve head, ethnic background, a positive family history for glaucoma, stage of the disease, and high myopia.<sup>[7]</sup> In recent years, findings have suggested that serum 25-OH vitamin D levels are associated with glaucoma.<sup>[8]</sup>

In recent years, evidence is also emerging regarding the relationship between vitamin D deficiency and ocular diseases. It has been shown to be associated with myopia,<sup>[9]</sup> age-related macular degeneration,<sup>[10]</sup> retinopathy,<sup>[11]</sup> uveitis,<sup>[12]</sup> retinoblastoma,<sup>[13]</sup> and dry eye.<sup>[14]</sup> Evidence is also emerging regarding the association between Vitamin D and glaucoma,<sup>[15]</sup> though the relationship has not yet been established fully. Additionally, experimental studies have also shown that neuroprotective functions in the central nervous system, including the optic nerve, are regulated by vitamin D.<sup>[16]</sup> Moreover, the association of vitamin D with various known risk factors for glaucoma like diabetes, hypertension, and dyslipidemia that have an association with the elevation of intraocular pressure and reduced blood flow<sup>[17,18]</sup> also indicates a secondary effect of vitamin D deficiency with the pathogenesis of glaucoma.

There is a potential physiological role for vitamin D as an anti-inflammatory agent in the oxidative stress-driven pathogenesis of primary open angle glaucoma.<sup>[19]</sup> Hence, the present study was planned with an aim to study the relationship between vitamin D and primary open angle glaucoma using a cross-sectional analytical design.

### MATERIAL AND METHODS

This is a Hospital-based case-control study, conducted in the department of ophthalmology, which included 92 subjects, between the age group of 40-70 years. The subjects were categorized as glaucomatous (46) and non-glaucomatous (46). Informed consent was obtained from all the patients in adherence to the tenets of the Declaration of Helsinki.

Patients of both groups underwent a comprehensive ophthalmic examination and detailed history of the patients was taken. A general and systemic examination of the patients was carried out. Both Uncorrected and best corrected visual acuity was recorded using Snellen's chart.

Anterior segment evaluation was done using slit-lamp examination. Goldmann's Applanation tonometer was used to measure the intraocular pressure of the patients. Fundus examination was carried out by ophthalmoscopy (direct and indirect) and also by using +90D. The visual field was analyzed by Humphrey's visual field analysis. After the visual field analysis, the patients were classified into early, moderate, and advanced categories based on visual field damage.

For vitamin D assessment, the 25 OH vitamin D levels were analyzed by using the Vitros immunoassay analyzer. The data was analyzed using Statistical Package for Social Sciences, version 21.0. Chi-square test, Independent samples 't'-test, and ANOVA were used to compare the data. and A 'p' value less than 0.05 was considered as significant.

### RESULT

The present study was conducted in a tertiary care hospital, to study the association between serum 25-OH vitamin D levels and severity of POAG. 92 subjects aged between 40-70 years, participated in this study which is a hospital-based case control study. The subjects were equally divided into cases and controls containing 46 subjects each. The mean age came out to be  $56.54 \pm 7.62$  for cases and  $55.98 \pm 10.15$  for controls. Out of 46 cases, 27 (58.7%) were male and the remaining 19 (41.3%) were females. In the control group, 22 (47.8%) were males and 24 (52.2%) were females. And the p value came out to be 0.296. [TABLE 1]

**Table 1: Comparison of Age and Gender Profile of Cases and Controls**

| S.N | Variable parameters | Cases (n=46) |            | Controls (n=46) |             | Statistical significance |       |
|-----|---------------------|--------------|------------|-----------------|-------------|--------------------------|-------|
| 1.  | MEAN AGE $\pm$ SD   | 56.54        | $\pm 7.62$ | 55.98           | $\pm 10.15$ |                          |       |
| 2.  | SEX                 | No.          | %          | No.             | %           | $\chi^2$                 | 'p'   |
|     | Male                | 27           | 58.7       | 22              | 47.8        | 1.092                    | 0.296 |
|     | Female              | 19           | 41.3       | 24              | 52.2        |                          |       |

POAG cases were divided into severity grades of glaucoma based on visual field defects. 19 early grade patients (41.3%) had a visual field mean deviation better than -6 dB, 16 moderate grade (34.7%) had visual field between -12 and <-6 and 11 advanced glaucomatous patients (24 %) had mean damage worse than -12 db. [TABLE 2]

**Table 2: Distribution of cases according to severity of Glaucoma**

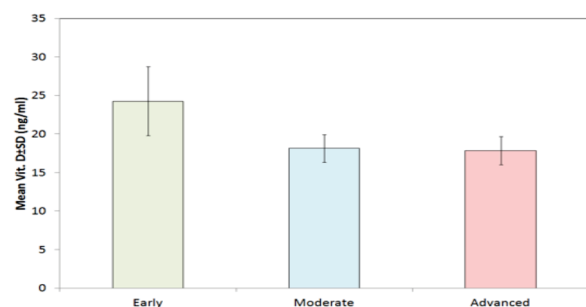
| SN | Grade    | Number | Percentage | Humphrey's mean visual field deviation |
|----|----------|--------|------------|----------------------------------------|
| 1. | Early    | 19     |            | -4 to -6                               |
| 2. | Moderate | 16     | 34.7       | <-6 to -12                             |
| 3. | Advanced | 11     | 24.0       | <-12 to -18                            |

A significant difference was observed between vitamin D levels of early grade (24.26 $\pm$ 4.47 ng/ml) and advanced grade (17.85 $\pm$ 1.85 ng/ml) POAG patients. And the vitamin D levels of moderate grade came out be 18.14 $\pm$ 1.79 ng/ml, which was statistically significant (p<0.001) [TABLE 3] and [FIGURE 1]

**Table 3: Comparison of Mean Vitamin D levels among different severity grades of Glaucoma**

| SN | Grade      | Number | Vitamin D levels ( ng/ml) |      |           |
|----|------------|--------|---------------------------|------|-----------|
|    |            |        | Mean                      | SD   | Range     |
| 1. | Early b,c  | 19     | 24.26                     | 4.47 | 20.2-31.7 |
| 2. | Moderate a | 16     | 18.14                     | 1.79 | 14.4-20.6 |
| 3. | Advanced a | 11     | 17.85                     | 1.85 | 14.8-21.4 |

F=21.15; p<0.001;



**Fig. 1: Comparison of Vitamin D levels among different grades of glaucoma**

Proportion of those with vitamin D deficiency was 0%, 87.5%, and 90.9% respectively in early, moderate and advanced stage of glaucoma. 73.1% of Early glaucoma had serum 25(OH) Vitamin D insufficiency in comparison to 12.5% in moderate and 9.1 % in Severe glaucoma. Sufficient value of Vitamin D was only seen in Early glaucoma. This shows a significant incremental trend of vitamin D deficiency with increasing stage of glaucoma. [TABLE 4] and [FIGURE 2]

**Table 4: Association between vitamin D levels and severity of glaucoma (Cases)**

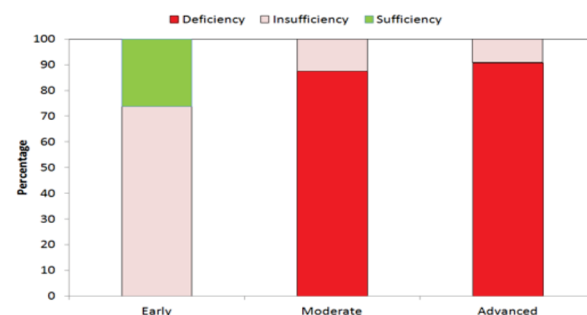
| SN | Vitamin D levels            | Early (n=19) |      | Moderate (n=16) |      | Severe (n=11) |      |
|----|-----------------------------|--------------|------|-----------------|------|---------------|------|
|    |                             | No.          | %    | No.             | %    | No.           | %    |
| 1. | Deficiency (<20 ng/ml)      | 0            | 0    | 14              | 87.5 | 10            | 90.9 |
| 2. | Insufficiency (20-30 ng/ml) | 14           | 73.7 | 2               | 12.5 | 1             | 9.1  |
| 3. | Sufficiency (>30 ng/ml)     | 5            | 26.3 | 0               | 0    | 0             | 0    |

2=35.84; p<0.001

## DISCUSSION :

The leading cause of irreversible blindness in the world is glaucoma. Primary Open Angle Glaucoma (POAG) is the most common type of glaucoma. POAG can be considered as a chronic, progressive optic

neuropathy characterised by cupping and atrophy of the optic disc, Visual Field (VF) loss, open angles, and no obvious ocular or systemic reason.<sup>[20]</sup>



**Fig. 2: Association between vitamin D levels and severity of glaucoma**

The rise in intraocular pressure (IOP) is considered to be an important factor responsible for glaucoma, however, recent studies undermine the role of IOP in open angle glaucoma.<sup>[21]</sup> In recent years vitamin D has been recognized to play an important role in ageing, inflammation and metabolic stress reduction.<sup>[22]</sup> Vitamin D is recognized as one of the key controllers of systemic inflammation, oxidative stress and mitochondrial respiratory function, and thus, the aging process in humans.<sup>[22]</sup> More and more evidence regarding the role of vitamin D in glaucoma is emerging, however, there is lack of consistent findings thus stressing upon the need to carry out more studies in order to potentiate this relationship with more evidence. Hence the present study was planned to study the relationship between vitamin D and primary open angle glaucoma.

In present study, glaucoma patients had significantly lower mean vitamin D levels (20.60 $\pm$ 4.41 ng/ml) as compared to controls (24.60 $\pm$ 5.89 ng/ml). Moreover, proportion of those with vitamin D deficiency was also significantly higher in cases (52.2%) as compared to that in controls (26.1%). These findings suggest a significant association of vitamin D deficiency with glaucoma. Lower vitamin D levels and higher vitamin D deficiency in glaucoma patients as compared to controls has been reported in various studies, however, there is considerable variability in the vitamin D levels among different studies.

Most of the studies have shown a significant association of vitamin D levels with glaucoma. Workers like Gonçalves *et al.*,<sup>[23]</sup> Kim *et al.*,<sup>[24]</sup> Vukovic Arar *et al.*,<sup>[25]</sup> Lv *et al.*<sup>[26]</sup> and Atalay *et al.*<sup>[27]</sup> similar to our study found mean vitamin D levels in glaucoma cases to be significantly lower as compared to controls without glaucoma. They also found the prevalence of vitamin D deficiency/insufficiency to be higher in cases<sup>[28]</sup> as compared to controls as observed in present study. Identification of vitamin D deficiency as a potent risk factor for open angle glaucoma has also been made by Yoo *et al.*<sup>[29]</sup> on multivariate assessment. As such association of vitamin D deficiency with factors associated with glaucoma pathogenesis have also been highlighted in different studies. Association of lower vitamin D levels with macular/retinal thinning,<sup>[30]</sup> ganglionic cell complex reduction<sup>[31]</sup> and corneal endothelial cell layer reduction<sup>[32]</sup> has been well-documented. A possible correlation between vitamin D levels and IOP has also been seen by Uçar *et al.* (2015)<sup>[33]</sup> in their study, thus showing a possible role of vitamin D in the pathogenesis of glaucoma.

However, there seem to be substantial differences in vitamin D levels in different studies. In case group, in present study, mean vitamin D level was 20.60 ng/ml. However, in different studies, they have been reported to vary from as low as 15.5 ng/ml<sup>[34]</sup> to as high as 26.37 ng/ml<sup>[35]</sup>. As such vitamin D levels show an extreme variability in different ethnicities. In the study by Malik *et al.*<sup>[36]</sup> mean vitamin D levels of blacks (21.39 ng/ml) were substantially lower than that of whites (26.62 ng/ml).

Malik *et al.*<sup>[36]</sup> in their study did not find a significant difference in mean vitamin D levels between glaucoma cases and controls in overall study population. In fact, in their study they found the mean levels in Blacks with glaucoma to be significantly higher as compared to those without glaucoma, thereby showing an inverse relationship. Uçar *et al.*<sup>[33]</sup> too in their study reported a significant positive correlation between IOP and

vitamin D levels thus showing higher vitamin D levels instead of lower ones were associated with higher IOP. However, as stated above, IOP is not the only factor affecting the glaucoma pathogenesis but it is a neurodegenerative chronic disorder affected by aging too<sup>[37]</sup>. A difference in age profile of patients in different studies could thus help in explaining the variability in vitamin D levels in different studies. Nevertheless, existence of higher vitamin D levels in control group of age and sex-matched non-glaucomatous populations in different studies underscores the relevance of vitamin D levels in the pathogenesis and progression of glaucoma. Lv *et al.* (2017)<sup>[26]</sup> compared serum 25(OH)D levels of 73 POAG patients and 71 age-matched controls of Han population in the age range 55 to 65 years (68 males, 76 females). Mean serum 25(OH)D levels were 30.43±3.91 ng/ml and 26.37±5.83 ng/ml respectively in controls and cases, thus showing that cases had significantly lower mean vitamin D levels as compared to controls.

In a study by Ayyagari *et al.*<sup>[38]</sup> they highlighted that vitamin D levels assume a significant role in advanced stage of glaucoma, thus showing that while pathogenesis of glaucoma could be ascribed to the age-related neurodegeneration, however, its progression is actively influenced by vitamin D levels. In present study we also observed that mean vitamin D levels were 24.26±4.47, 18.14±1.79 and 17.85±1.85 ng/ml respectively for early, moderate and advanced stages of glaucoma, thus showing that while mean values in early stage of glaucoma were quite close to control group (24.60 ng/ml) and thus we also endorse the observations made by Ayyagari *et al.*<sup>[38]</sup> that vitamin D levels hold more relevance in advanced or higher stages of glaucoma. We also found that cases with early stage of POAG did not have vitamin D deficiency as compared to 87.5% and 90.9% of those with moderate and advanced glaucoma. These findings thus highlight the role of vitamin D deficiency in glaucoma progression. The findings also highlight the importance of vitamin D supplementation as a protective measure against progression of glaucoma.

## CONCLUSION

The findings of the study showed that vitamin D levels were in general lower in glaucoma patients. It was also showed that a significant association between low vitamin D levels and higher severity of glaucoma was observed. The findings of present study thus denote a significant role of vitamin D in pathogenesis and progression of glaucoma. Further longitudinal studies are recommended to evaluate the association of vitamin D with glaucoma pathogenesis and progression as well as those evaluating role of vitamin D supplementation as a preventive measure are also recommended.

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## Conflict of interest :

No potential conflict of interest relevant to this article was reported.

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