

# Association of Vitamin D deficiency with primary glaucoma among Saudi population – A pilot study

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## Abstract:

**PURPOSE:** Glaucoma is a complex multifactorial disorder that is influenced by various systemic conditions. Several studies investigated the association between systemic factors such as Vitamin D deficiency for glaucoma development and reported contradicted findings. The aim of this study was to assess Vitamin D levels in glaucomatous Saudi subjects and its association with cup/disc ratio in primary open- and closed-angle glaucoma.

**METHODS:** This was a pilot study that included subjects aged 41–78 years from both genders recruited from a tertiary hospital, Riyadh city, Kingdom of Saudi Arabia. Subjects were divided into three groups: Group 1: subjects with primary open-angle glaucoma (POAG), Group 2: subjects with primary angle-closure glaucoma (PACG), and Group 3: control subjects. All participants underwent detailed ophthalmic examinations including visual acuity, intraocular pressure measurement (IOP), gonioscopy, and fundus examinations. In addition, blood samples were collected from glaucoma patients and controls to measure the serum 25-hydroxyvitamin D levels.

**RESULTS:** A total of 75 subjects were included in this study. Measurement of IOP was within the range of 9–27 for all subjects. Mean serum 25-hydroxyvitamin D levels were  $72.58 \pm 31.79$ ,  $69.20 \pm 24.24$ , and  $67.14 \pm 29.02$  in Groups 1, 2, and 3, respectively. There were insignificant differences in Vitamin D levels among the three groups ( $P > 0.05$ ). Moreover, no significant correlation was noted between Vitamin D levels and cup/disc ratio in Groups 1 and 2.

**CONCLUSION:** No association was found between Vitamin D deficiency and both POAG and PACG among Saudi population despite low serum level of Vitamin D in glaucomatous and control subjects. This study suggested that Vitamin D level may not contribute in augmenting the severity and progression of glaucoma.

## Keywords:

Cup/disc ratio, primary angle closure, primary open-angle glaucoma, Vitamin D.

## INTRODUCTION

Glaucoma is a distinctive optic neuropathy characterized by gradual functional degeneration and deterioration of optic nerve, resulting in progressive diminution of visual functions resulting in irreversible field loss.<sup>[1]</sup> It is the second worldwide leading cause of blindness.<sup>[2-7]</sup> Glaucoma prevalence is variable among different regions worldwide, due to many factors including age, gender, and ethnicity.<sup>[7]</sup> The prevalence of primary open-angle glaucoma (POAG) is highest in

Africa (4.2%); meanwhile, primary angle-closure glaucoma (PACG) is highest in Asia (1.09%).<sup>[4]</sup> In the Kingdom of Saudi Arabia (KSA), for example, primary glaucoma represented two-thirds of glaucoma cases. The POAG is the preponderant type of glaucoma (30.5%), whereas PACG is the second common type (24.7%) of all cases.<sup>[8]</sup> Thus, there is a need for population-based studies in KSA for future intervention.

Vitamin D (calciferol) is a fat-soluble essential vitamin that is activated by the kidney to enhance the essential intestinal absorption of calcium and phosphorous, required for normal bone mineralization, muscle contraction, and nerve

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conduction.<sup>[9,10]</sup> Vitamin D and its ocular receptors control various genes entangled in immunity, inflammation, cellular growth, differentiation, and programmed cell death.<sup>[11]</sup> Many studies demonstrated that levels of Vitamin D and genetic variations can impact variable ocular conditions such as dry eye,<sup>[12-14]</sup> myopia,<sup>[15]</sup> age-related macular degeneration,<sup>[16,17]</sup> and glaucoma.<sup>[18-24]</sup>

The association of Vitamin D deficiency with glaucoma was investigated in previous studies. It found that decreased serum 25-OHD concentration was associated with the presence but not the severity of POAG.<sup>[21]</sup> It was suggested that Vitamin D deficiency should be considered a potential risk factor for the development of open-angle glaucoma.<sup>[19,25,26]</sup> Despite the high prevalence of both glaucoma and Vitamin D deficiency in KSA, there is no studies that investigated the association between Vitamin D and glaucoma among this population. Thus, the aim of this study was to assess Vitamin D levels in glaucomatous Saudi subjects and its association with cup/disc (C/D) ratio in primary open- and closed-angle glaucoma.

## METHODS

This study was designed as a cross-sectional randomized case-control study that included subjects aged between 41 and 78 years with glaucoma from both genders. Subjects were recruited from a tertiary hospital, Riyadh city, KSA, in the period from March to November 2018. This study was approved by the Ethics Committee of Deanship of Scientific Research at King Saud University. The protocol of the study was explained to each participant at the time of recruitment, and informed consent was obtained according to the Declaration of Helsinki.

Subjects were divided into three groups: Group 1: subjects with POAG, Group 2: subjects with PACG, and Group 3: healthy controls recruited from anterior segment clinics who attend for routine ocular examination. Inclusion criteria included subjects aged  $\geq 40$  years without diabetes mellitus who were diagnosed with POAG or PACG with no other associated intraocular pathology and no family history of glaucoma as confirmed from patients' hospital records.

Diagnostic criteria for POAG included open anterior chamber angle, high intraocular pressure (IOP)  $> 21$  mmHg, glaucomatous optic nerve damage (cupping) with corresponding visual field loss as the damage progresses with the absence of signs of secondary glaucoma, or a nonglaucomatous optic neuropathy.<sup>[27-29]</sup> However, elevated IOP is not always related to POAG, because in some conditions as in normal-tension glaucoma, all the previous characteristics are present with normal IOP level ( $< 21$  mmHg).<sup>[27,30]</sup>

Diagnostic criteria for PACG included closed anterior chamber angle which can occur either by temporary apposition of the peripheral iris to the trabecular meshwork or by permanent adhesions in the angle of the anterior chamber (peripheral anterior synechiae). In addition, pupillary block is the most

common mechanism of PACG that causes obstruction of aqueous humor to flow freely from the posterior chamber, through the pupil, and into the anterior chamber. Aqueous humor accumulates behind the iris increasing its convexity that results in narrowing of anterior chamber angle. In some cases, patients may present with acute primary angle closure, characterized by conjunctival hyperemia, corneal edema, a mid-dilated nonreactive pupil, a shallow anterior chamber, and high IOP, usually  $> 30$  mmHg. Those patients often complain of ocular pain, nausea, vomiting, and intermittent blurring of vision with haloes seen around lights.<sup>[31]</sup>

Exclusion criteria were: high myopia, retinal diseases, intraocular inflammation, trauma, and chronic diseases with altered Vitamin D level as cardiovascular diseases, autoimmune disorders, renal disease, infectious diseases and tumors. In addition, subjects using medications such as systemic corticosteroids, immunosuppressant, or Vitamin D supplement were excluded from the study.

All participants were subjected to complete ophthalmic examinations inclusive of visual acuity test measured by Snellen (E) chart, IOP assessed using Goldmann applanation tonometry, anterior chamber angle structure and depth examination using gonio lens, and fundus examination by noncontact auxiliary lens (VOLK) to permit a stereoscopic fundus view. This method assessed any characteristic glaucomatous structural alterations including cupping of optic disc, hemorrhages, and defects in retinal nerve fiber layer. Humphrey visual field analyzer was used to assess the visual field of glaucomatous patients. In addition, posterior segment optical coherence tomography 3D-OCT 2000 was used for evaluation of glaucomatous structural damage.<sup>[24]</sup>

Serum levels of 25-hydroxyvitamin D were measured for all participants. Five milliliters of venous blood were collected from all participants in a labeled yellow-top blood tube with gel (without anticoagulant). Centrifugation of blood was performed to separate the serum for biochemical analysis using Electrochemiluminescence ECL (COBAS 6000-E 601). This technology is for heterogeneous immunoassays that use micromagnetic particles to catch the antigen-antibody complex to electric source measuring the serum 25-hydroxyvitamin D level by photon machine. The normal level of serum 25(OH) D in adults should be ranged between 30 and 80 ng/mL (75–200 nmol/L), while in Vitamin D deficiency, it is recognized to be  $< 20$  ng/mL (50 nmol/L).

One-way ANOVA test was applied to study different measured variables of participants including ages, ophthalmic parameters, and Vitamin D levels among groups. As IOP was not normally distributed, Kruskal-Wallis test was performed to compare IOP between different groups. For the association between C/D ratio and Vitamin D, Spearman correlation coefficient test was performed with 95% confidence interval, assuming the Vitamin D level (independent variable) and the C/D ratio (dependent variable). The probability values of  $P < 0.05$  were considered statistically significant. The statistical analyses were performed

using IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

## RESULTS

Seventy-five subjects were recruited for the study. They were divided in three groups: (1) Group 1 = 27 subjects with POAG, (2) Group 2 = 23 subjects with PACG, and (3) Group 3 = 25 sex- and age-matched healthy controls. Table 1 reveals the demographic information (age and gender) and ophthalmic measurements obtained from all the groups. There was insignificant difference ( $P > 0.05$ ) in age and gender in the three studied groups. Since there were no significant differences in measured parameters between both eyes ( $P > 0.05$ ), data of right eye were considered for the statistical analysis. Table 1 demonstrates no statistically significant difference ( $P > 0.05$ ) between the three groups in uncorrected and corrected distance visual acuity (UCDVA), CDVA, and IOP. However, a statistically significant difference ( $P < 0.0001$ ) was found in C/D ratio between controls and glaucoma groups, with no statistically significant difference observed between the POAG and PACG groups in C/D ratio ( $P > 0.05$ ). C/D ratio in the glaucoma groups was higher relative to controls.

The mean  $\pm$  standard deviation of serum levels of 25-hydroxyvitamin D were  $72.58 \pm 31.79$  nmol/L in the POAG group,  $69.20 \pm 24.24$  nmol/L in the PACG group, and  $67.14 \pm 29.02$  nmol/L in the control group. Most of the subjects in all the groups had low normal levels of Vitamin D. However, subjects in the POAG group had an acceptable borderline level of Vitamin D while controls had the lowest level of Vitamin D followed by PACG group. Overall, no statistically significant differences were noted in serum levels of 25-OHD between the three studied groups [ $P > 0.05$ ; Table 1 and Figure 1].

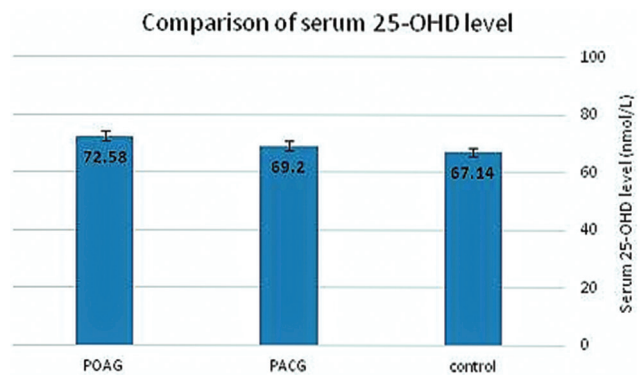
The correlation between demographic factors (i.e., age and gender) and Vitamin D level was also tested in all the groups, but no correlation was found ( $P > 0.05$ ), which indicates that these factors did not affect 25-hydroxyvitamin D serum level. The results also revealed insignificant relation between Vitamin D levels and C/D ratio in each group as the correlation coefficient ( $r$ ) was  $-0.1080$ ,  $0.072$ , and  $-0.219$  in POAG, PACG, and controls, respectively,  $P > 0.05$  in all the groups [Figures 2 and 3].

## DISCUSSION

It was hypothesized that level of Vitamin D is low significantly in glaucoma subjects than controls. Conversely, this study found no significant difference in serum 25-OHD level between POAG, PACG, and controls. Similarly, Li *et al.* assessed the correlation of Vitamin D and different types of glaucoma including POAG among Chinese population and found no significant differences ( $P = 0.064$ ) of serum Vitamin D levels between POAG and controls.<sup>[32]</sup> The control and PACG groups in the present study had Vitamin D deficiency, while the POAG group had an acceptable borderline level of Vitamin D [Figure 1].

In contrast, previous studies<sup>[18,20,21]</sup> demonstrated that level of 25-OHD was significantly higher ( $P < 0.001$ ) in age-matched controls than in POAG. The variation between present findings and previous studies may be due to high prevalence of Vitamin D deficiency in Saudi population, especially in the elderly.<sup>[33-35]</sup> The age of participants ranged between 41 and 78 years which was consistent with that of participants in previous studies. This indicates that age was not a variant factor that could contribute in reducing the level of serum 25-OHD. However, it is known that elderly people are at high risk of Vitamin D deficiency as aging contributes to decrease concentrations of 7-DH (7 Dehydrocholesterol) in the skin, which reduce cutaneous ability to synthesize Vitamin D.<sup>[36]</sup>

In the current study, ophthalmic parameters were not significantly different among groups. The measurement of IOP

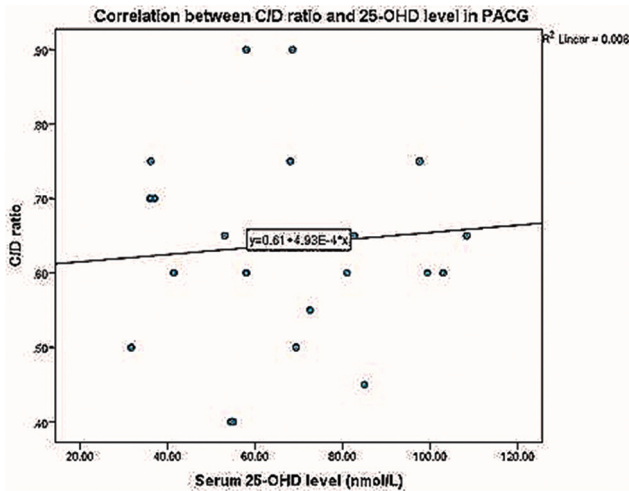


**Figure 1:** Comparison of serum 25-OHD (nmol/L) level in Control, POAG and PACG groups

**Table 1: Demographic and ocular parameters measured in the three studied groups**

Parameters	POAG (n=27)	PACG (n=23)	Control (n=25)	P
Gender (female), n (%)	16 (59.2)	12 (52.2)	13 (52)	>0.05
Age (mean $\pm$ SD)	58.26 $\pm$ 9.55 (42-77)	61.04 $\pm$ 8.29 (43-71)	58.64 $\pm$ 10.62 (41-78)	0.7578
UCDVA (LogMAR) 0-1.7	0.40 $\pm$ 0.30	0.47 $\pm$ 0.46	0.44 $\pm$ 0.40	0.9697
CDVA (LogMAR) 0-0.6	0.01 $\pm$ 0.03	0.02 $\pm$ 0.04	0.10 $\pm$ 0.19	0.2954
IOP (mmHg)	16.30 $\pm$ 4.02 (10-27)	15.56 $\pm$ 4.52 (9-31)	16.26 $\pm$ 3.09 (10-24)	0.9562
C/D	0.63 $\pm$ 0.14 (0.4-0.9)	0.64 $\pm$ 0.13 (0.4-0.9)	0.32 $\pm$ 0.07 (0.2-0.5)	<0.0001*
25-OHD (nmol/L)	72.58 $\pm$ 31.79 (22-167)	69.20 $\pm$ 24.24 (31-108)	67.14 $\pm$ 29.02 (18-145)	0.7259

Data presented as mean $\pm$ SD. Significant value presented in bold. POAG: Primary open-angle glaucoma, PACG: Primary angle-closure glaucoma, UCDVA: Uncorrected distance visual acuity, CDVA: Corrected distance visual acuity, IOP: Intraocular pressure, C/D: Cup-to-disc ratio, 25-OHD: 25-hydroxyvitamin D, SD: Standard deviation, LogMAR: Logarithm minimum angle of resolution, \*: Highly significant



**Figure 2:** Correlation between vitamin D levels with the C/D ratio in POAG subjects. This graph shows no significant correlation,  $P = 0.593$

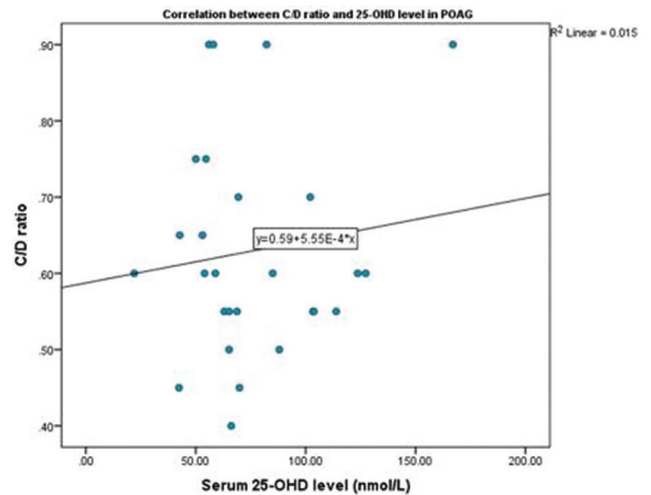
was controlled in POAG and PACG. There was no difference between C/D ratio in POAG and PACG which is consistent with Ngo *et al.* who proved that optic disc rim area, volume, and vertical C/D ratio showed insignificant difference between POAG and PACG.<sup>[37]</sup>

Although C/D ratio is a widely used diagnosis and staging of glaucoma, the measure has some limitations. Tatham *et al.* suggested that assessment of C/D ratio is an insensitive measure for assessment of progressive neural losses in glaucoma. Even relatively small changes in C/D ratio could be associated with large losses of retinal ganglion cells (RGCs), particularly in large C/D ratios.<sup>[38]</sup> Thus, assessment of C/D ratio measurements should not be used as the sole method for detection of glaucomatous progression. In contrast, assessment of the retinal nerve fiber layer measurements with imaging technologies could be used to detect much smaller losses of RGCs over time.

Although it was hypothesized that low concentration of serum 25-OHD might cause additional optic disc damage in glaucomatous patients, the current study did not show a relationship between level of Vitamin D and C/D ratio in POAG and PACG [Figures 2 and 3]. This was confident with Goncalves *et al.* who found that serum 25-OHD level and C/D ratio in patients with POAG were not correlated.<sup>[21]</sup> However, Yoo *et al.* demonstrated a significant correlation ( $P < 0.05$ ) between C/D ratio and serum 25-OHD level among POAG individuals.<sup>[19]</sup> Thus, the current study suggests that Vitamin D level may not contribute to augmenting the severity and progression of glaucoma.

## CONCLUSION

Although the sample of adults glaucomatous and controls had low serum level of Vitamin D, no correlation was proved between deficiency of Vitamin D and both POAG and PACG among Saudi population. Further longitudinal studies



**Figure 3:** Correlation between vitamin D levels with the C/D ratio in PACG subjects. This graph shows no significant correlation,  $P = 0.745$

are planned to show the effect of intervention (Vitamin D supplements) on glaucoma progression.

Although subjects were recruitment randomly, selection bias is unavoidable. That's why it is important to examine study design for this type of bias and find ways to adjust for it.

The authors declare no potential conflicts of interest with respect to the authorship, and/or publication of this article.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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