

The Analysis Study of Effectiveness of Vitamin D Supplementation for Prevention of Open Angle Glaucoma: A Comprehensive Systematic Review

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ABSTRACT

Background: Over 70 million people worldwide suffer from glaucoma. Over the next 20 years, this is anticipated to rise to 111 million. Primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) are the two principal subtypes of glaucoma. The most prevalent glaucoma subtype is POAG. **The aim:** The aim of this study to show about effectiveness of vitamin D supplementation for prevention of open angle glaucoma. **Methods:** By the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. This search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed, SagePub, and Sciencedirect were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done. **Result:** Seven publications were found to be directly related to our ongoing systematic examination after a rigorous three-level screening approach. Subsequently, a comprehensive analysis of the complete text was conducted, and additional scrutiny was given to these articles. **Conclusion:** Despite being mostly unknown, the relationship between vitamin D and POAG is particularly intriguing because, when taken as directed, vitamin D is a reasonably priced and safe supplement. It seems that vitamin D protects against oxidative damage and the generation of reactive oxygen species (ROS). Consequently, hypotheses linking vitamin D to POAG include the vitamin's antioxidant properties and its function in inhibiting inflammatory gene expression.

Keywords: Primary open-angle glaucoma (POAG), Vitamin D, Prevention, Supplementation.

INTRODUCTION

Peripheral and occasionally central vision loss result from glaucoma, a chronic progressive optic neuropathy marked by damage to the optic nerve head (ONH) and retinal nerve fiber layer (RNFL). Older age, high intraocular pressure, sub-Saharan African ethnicity, positive family history, and high myopia are risk factors for primary open-angle glaucoma, the most prevalent type of glaucoma. The chief risk factors for primary angle-closure glaucoma are East Asian ethnicity, hyperopia, and advanced age. This illness has the potential to cause irreversible blindness if left untreated. Glaucoma continues to be a leading cause of blindness worldwide.^{1,2}

To better understand the pathophysiology of glaucoma, more attention must be paid to environmental or lifestyle factors, such as dietary patterns and their relationship to the condition. More and more research has looked into the connection between glaucoma and dietary intake, particularly vitamin

intake. Numerous studies have indicated that oxidative stress-mediated glaucoma or intraocular pressure (IOP), the only modifiable risk factor for glaucoma, may be influenced by nutrition. When more reactive oxygen species are produced than the cell's anti-oxidative capacity can withstand, oxidative stress results. This damages the trabecular meshwork, the eye's aqueous humour outflow system, raising intraocular pressure and eventually leading to the death of retinal ganglion cells.^{1,3,4}

Numerous research have lately asserted an inverse relationship between IOP and glaucoma and vitamin D3 levels in its hydroxylated form (25-hydroxyvitamin D3 or calcifediol, abbreviated 25(OH)D3). It is true that it is exceedingly challenging for clinical laboratories to quantify vitamin D levels directly in serum or plasma. Since the majority of vitamin D generated in the body is converted to 25(OH)D and its measurement is possible, 25(OH)D levels are measured.^{5,6}

Glaucoma, a class of visual neuropathies characterized by the

death of retinal ganglion cells (RGCs) and the loss of their axons, is a major cause of permanent blindness. Vitamin D insufficiency has been linked to glaucoma, according to two cross-sectional studies conducted in South Korea. In a similar vein, a Chinese study discovered that vitamin D deficiency, the existence of the VDR gene's BsmI "B" allele, and the TaqI "t" allele are significant risk factors for the development of glaucoma. Serum vitamin D levels are lower in glaucoma patients than in normal controls, according to other research conducted in France, Croatia, the US, and Turkey. Serum vitamin D levels did not, however, differ statistically significantly between glaucoma patients and control people, according to another Turkish case-control study. In a similar vein, a recent large-sample study conducted in the United States revealed no significant correlation between the incidence of glaucoma and vitamin D serum levels, food intake, or supplementation.^{7,8}

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast effectiveness of vitamin D supplementation for prevention of open angle glaucoma. It is possible to accomplish this by researching of the effectiveness of vitamin D supplementation for prevention of open angle glaucoma. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about the effectiveness of vitamin D supplementation for prevention of open angle glaucoma.

In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used "effectiveness of vitamin D supplementation for prevention of open angle glaucoma." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed, SagePub, and Sciencedirect databases.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The

writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and cannot have been seen anywhere else.

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review

depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

Table 1. Search Strategy

<i>Database</i>	<i>Search Strategy</i>	<i>Hits</i>
Pubmed	((("Open angle glaucoma"[MeSH Subheading] OR "Vitamin D"[All Fields] OR "TPrevention" [All Fields]) AND ("Supplementation" [All Fields]))	77
Science Direct	((("Open angle glaucoma"[MeSH Subheading] OR "Vitamin D"[All Fields] OR "TPrevention" [All Fields]) AND ("Supplementation" [All Fields]))	483
Sagepub	((("Open angle glaucoma"[MeSH Subheading] OR "Vitamin D"[All Fields] OR "TPrevention" [All Fields]) AND ("Supplementation" [All Fields]))	114

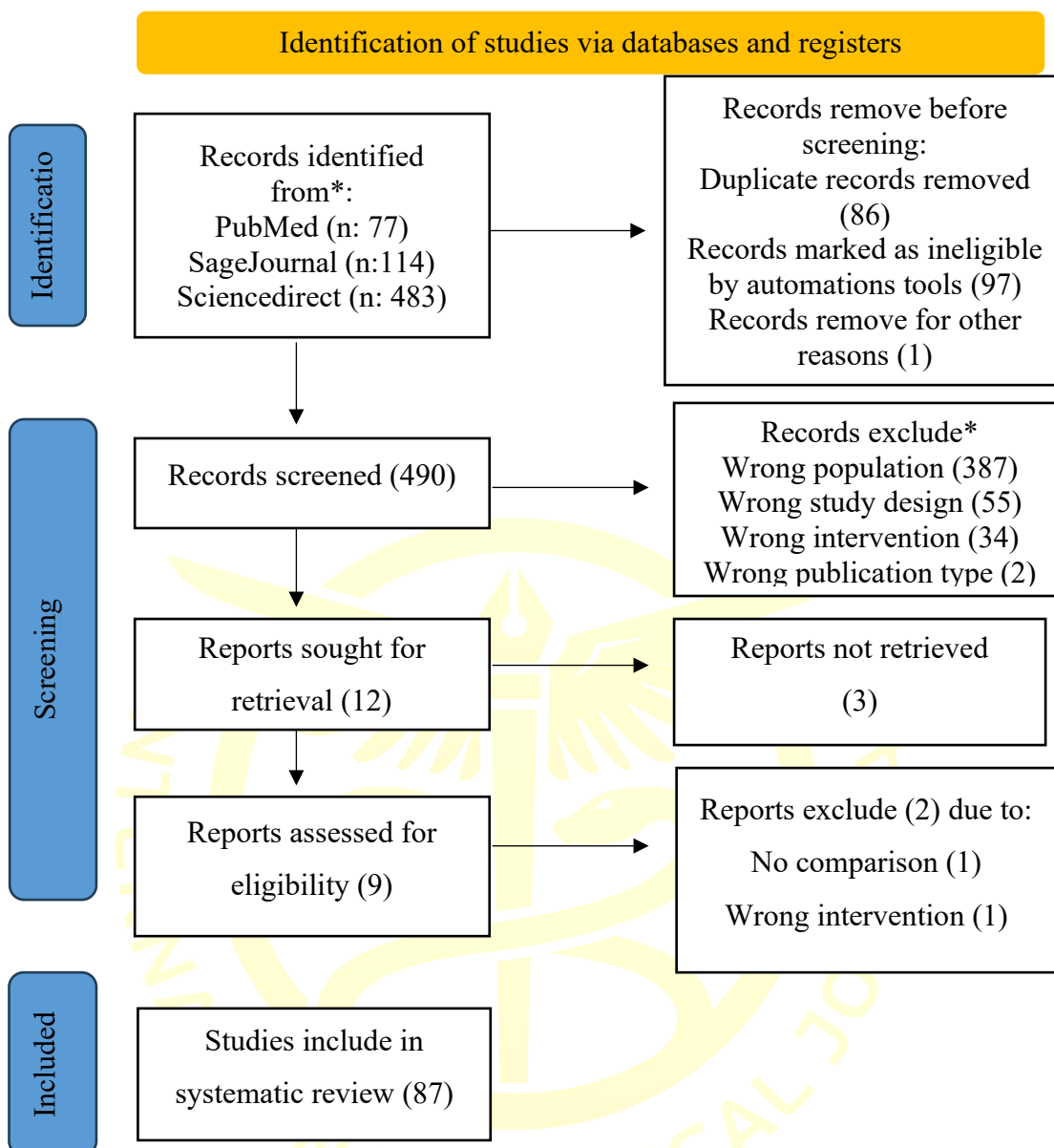


Figure 1. Article search flowchart

Table 2. Critical appraisal of Study

Parameters	(Kanso, N et al., 2024)	(Bokhary, KA et al., 2022)	(Ayyagari, R et al., 2019)	(Yoo, TK et al., 2014)	(Malik, A et al., 2024)	(Lv, Y et al., 2016)	(Sale, m, TI et al., 2023)
1. Bias related to temporal precedence							
Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Bias related to selection and allocation							
Was there a control group?	No	No	Yes	No	No	Yes	Yes
3. Bias related to confounding factors							
Were participants included in any comparisons similar?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Bias related to administration of intervention/exposure							
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	No	No	No	No	No	No	No
5. Bias related to assessment, detection, and measurement of the outcome							
Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	No	No	No	No	No	No	No
Were the outcomes of participants included in any comparisons measured in the same way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Bias related to participant retention							
Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Statistical conclusion validity							
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

RESULT

Using reputable resources like Science Direct, PubMed, and SagePub, our research team first gathered 674 publications. A thorough three-level screening strategy was used to identify only seven papers as directly relevant to our ongoing systematic evaluation. Next, a thorough study of the entire text and further examination of these articles were selected. Table 3 compiles the literature that was analyzed for this analysis in order to make it easier to view.

Table 3. The litelature include in this study

Author	Origin	Method	Sample	Result
Kanso, N et al., 2024⁹	UK	We evaluated the causal relationship between vitamin D levels and vitamin D deficiency and primary open-angle glaucoma (POAG) using two-sample Mendelian randomization (MR) studies on data from the UK Biobank and the SUNLIGHT consortium.	79366	Neither vitamin D deficiency (OR = 0.980, 95% CI 0.928 to 1.036, p = 0.471) nor vitamin D levels (OR = 1.146, 95% CI 0.873 to 1.504, p = 0.326) were statistically associated with a higher risk of POAG. There was no evidence of a correlation between SNPs for genes involved in important steps of vitamin D metabolism and POAG, according to sensitivity analyses that included a more lenient p-value threshold, the use of only winter-measured samples, replication in the FinnGen dataset, and investigation of particular genetic markers.
Bokhary, KA et al., 2022¹⁰	Saudi Arabia	Participants in this pilot study, who were recruited from a tertiary hospital in	75	This study involved 75 individuals in total. All subjects' IOP measurements fell between 9 and 27. Groups 1, 2, and 3 had mean

		Riyadh, Kingdom of Saudi Arabia, ranged in age from 41 to 78 years and were of both sexes.		blood 25-hydroxyvitamin D levels of 72.58 ± 31.79 , 69.20 ± 24.24 , and 67.14 ± 29.02 , respectively. The three groups' vitamin D levels did not differ significantly from one another ($P > 0.05$). Furthermore, in Groups 1 and 2, there was no discernible relationship between vitamin D levels and cup/disc ratio.
Ayyagari, R et al., 2019 ¹¹	USA	This investigation included 178 normal controls with self-reported AD and 357 patients with a diagnosis of POAG, which were a subgroup of the AD and glaucoma assessment study III (ADAGES III) cohort.	178	The visual field MD of the 179 participants with advanced glaucoma was worse than -10 dB, while the visual field MD of the 178 early POAG subjects was better than -4.0 dB. The subjects in the early phenotype (7.56 ± 5.74 pg/ml) and control (8.02 ± 6.19 pg/ml) groups had mean (95% CI [CI]) vitamin D levels that were significantly or marginally significantly different from those of the advanced phenotype (6.35 ± 4.76 pg/ml; $p = 0.0117$ and 0.0543 , respectively). Conversely, there was no significant difference in the mean serum vitamin D level between the participants with the early glaucoma phenotype and the controls ($p = 0.8508$).
Yoo, TK et al., 2014 ¹²	South Korea	Cross-sectional study.	6094	In quintiles of decreasing 25(OH)D, the multivariable-adjusted odds ratios of OAG were 1.26, 1.00 (reference), 1.31, 1.36, and 1.69 (P

				for quadratic trend <0.01). Compared to the second quintile, the odds ratio for the lowest 25(OH)D quintile was considerably larger ($P < 0.01$). Furthermore, we found a substantial correlation between the 25(OH)D level and predictors for deteriorating OAG, such as intraocular pressure or vertical and horizontal cup-to-disc ratios.
Malik, A et al., 2024¹³	Pakistan	This cross-sectional, observational study was conducted at Watim Medical College's Department of Ophthalmology and Department of Biochemistry in Rawat, Rawalpindi.	150	There was no statistically significant difference between the mean vitamin D levels in Group I (POAG) and Group II (Controls), which were 39.75 ± 9.64 ng/ml and 38.22 ± 7.59 ng/ml, respectively.
lv, Y et al., 2016¹⁴	China	In the Han population, 73 POAG patients and 71 age-matched controls were included. The enzyme-linked immunoabsorbent test was used to	144	Patients with primary open-angle glaucoma had lower serum levels of 1a, 25-Dihydroxyvitamin than age-matched controls. Statistical analysis revealed a significant difference in the allelic frequencies of the BsmI and TaqI genotypes between primary open-angle glaucoma patients and age-matched controls,

		measure the serum levels of 1a, 25-Dihydroxyvitamin D3.		while other polymorphisms did not show any significant differences.
Salem, TI et al., 2023¹⁵	Egypt	A total of 25 POAG patients and 25 control persons participated in this case-control research.	50	The control group's mean serum vitamin D level was 49.62 ng/mL ($\pm$ 11.42), but the POAG group's was 27.16 ng/mL ($\pm$ 11.53). Vitamin D was a highly effective discriminator between the two groups, according to ROC analysis (AUC = 0.926, 95% CI: 0.844–1.000). With a cut-off value of $\leq$ 16.32 ng/mL, vitamin D can predict severe POAG (AUC = 0.947, 95% CI: 0.858–1.000). According to logistic regression analysis, a major predictor of POAG was lower vitamin D levels. In multivariable analysis, only vitamin D levels were a predictor for higher grades of POAG severity, according to ordinal regression analysis.

DISCUSSION

About 10% of cases of legal blindness reported in the US are due to glaucoma, one of the main causes of irreversible blindness in the globe. The primary cause of glaucoma is increased intraocular pressure (IOP), which damages retinal ganglion cell axons—which transmit visual information from the eye to the brain—in an irreversible manner. Angle-closure glaucoma (ACG) and open-angle glaucoma (OAG) are the two types of glaucoma that can be distinguished by the mechanism that raises intraocular pressure. OAG is distinguished by greater resistance in the trabecular meshwork (TM), which raises IOP in contrast to ACG's narrow iridocorneal angle. According to a number of studies, TM resistance may be increased by variations in the quantity of several substances in aqueous humor, including endothelin-1, transforming growth factor β (TGF- β), hyaluronic acid, and vitamin C.^{16,17}

Until two-step hydroxylation takes place, vitamin D does not show biological activity. The vitamin D

metabolite is transferred to the kidneys where it is transformed into $1\alpha, 25$ -dihydroxyvitamin D [$1\alpha, 25(\text{OH})_2\text{D}$], an active form of vitamin D, after the liver hydroxylates vitamin D to 25-hydroxy vitamin D [$25(\text{OH})\text{D}$]. $25(\text{OH})\text{D}$ concentrations are typically measured to assess vitamin D status. Although its deficit impacts the metabolism of minerals and bones, current research has shown that vitamin D deficiency is linked to a number of systemic illnesses. Myocardial infarction, stroke, diabetes mellitus types 1 and 2, viral or chronic respiratory disorders, and autoimmune diseases can all be avoided with a healthy vitamin D consumption. Additionally, the prevalence or occurrence of eye conditions such diabetic retinopathy, age-related macular degeneration, myopia, and dry eye syndrome has been connected to serum vitamin D concentrations. Specifically, a number of studies have shown a correlation between OAG and the serum level of vitamin D.^{16,18}

According to the current literature it is likely that oxidative stress also plays a role in the

pathogenesis of glaucoma. Systemic oxidative stress is associated with decreased ocular blood flow. This association is related to the vascular permeability and results in a release of endothelin and nitric oxide (both oxidants). Blood levels of endothelin-1 have found to be significantly higher in patients with POAG. The association of nitric oxide with glaucoma has been reported before. Thus the nitrate-nitrite-nitric oxide pathway may play an important role in POAG. Nitrate is a source of nitric oxide and available in dark green leafy vegetables. In addition to nitrate, dark green leafy vegetables are also rich in vitamin A, C, and K. The present review suggested a beneficial association of vitamin A and C with OAG, but studies on vitamin K vs. OAG are currently lacking. Thus dark green leafy vegetables contain several relevant nutrients for OAG. This is emphasized by the fact that all retrieved studies on the association of green leafy vegetables with OAG found a significant association.^{19,20}

Vitamin D3, a vital hormone with anti-fibrotic and antioxidant

qualities, is one such molecule. Vitamin D3 deficiency is thought to be the cause of the ECM alterations in the TM observed in the pathophysiology of POAG. It is well known that vitamin D3 levels in the serum and AqH of individuals with POAG can be much lower than those in normal populations. The use of vitamin D3 as an antifibrotic agent in the ocular environment—more especially, the TM—will be examined in this review.^{21,22}

Krefting et al. conducted a study in Norway wherein they separated healthy Caucasians with high or low serum 25(OH)D levels into two groups. The IOP of the 87 participants with low serum 25(OH)D levels (mean 40.1 ± 12.9 nmol/l) did not differ from the IOP of the 42 participants with high serum 25(OH)D levels (mean 85.1 ± 14.0 nmol/l) (15.9 ± 3.3 versus 15.6 ± 3.1 mmHg, $p = 0.56$, independent t-test). The authors then conducted a randomized clinical trial and assessed the change in IOP following administration of either high dose vitamin D (one capsule of vitamin D3 20,000 IU-Dekristol; Mibe, Brehna,

Germany) or placebo twice a week for six months. These patients had low 25(OH)D at baseline, and the levels they reached after taking supplements for six months were significantly higher than those of the placebo group (142.7 ± 25.3 nmol/l versus 41.7 ± 14.2 nmol/l, $p < 0.01$ for difference in delta values between groups).^{5,23}

Although there is still disagreement about what constitutes low vitamin D status, there seems to be growing agreement that circulating 25(OH) D levels below ~30–32 ng/mL (~75–80 nmol/L) signify less than optimal vitamin D status. According to the American Geriatric Society, National Osteoporosis Foundation, Endocrine Society, and WHO, vitamin D deficiency is defined as a serum 25(OH)D level less than 20 ng/mL (50 nmol/L) and vitamin D insufficiency as a level between 21 and 30 ng/mL (51–75 nmol/L). Although serum total 25(OH)D concentration should be reported in nanomoles per litre (nmol/L) in accordance with international measurement standards, the unit nanograms per millilitre (ng/mL) is frequently used, especially

in the USA. A reference for total serum 25(OH)D levels that are "deficient," "insufficient," and "adequate" in terms of both nmol/L and ng/mL. This is important from a clinical standpoint since 800 IU of vitamin D per day is needed to raise the minimum blood 25(OH)D level to 20 ng/mL (50 nmol/L),⁴⁷ whereas 4000 IU per day is needed to raise the minimum level to 30 ng/mL (75 nmol/L). According to these two distinct cutoff values, the prevalence of vitamin D deficiency is <20 ng/mL (50 nmol/L) and <30 ng/mL (75 nmol/L).^{24,25}

CONCLUSION

In conclusion, despite being mostly unknown, the relationship between vitamin D and POAG is particularly intriguing because, when taken as directed, vitamin D is a reasonably priced and safe supplement. It seems that vitamin D protects against oxidative damage and the generation of reactive oxygen species (ROS). Consequently, hypotheses linking vitamin D to POAG include the vitamin's antioxidant properties and its function

in inhibiting inflammatory gene expression.

DISCLOSURE STATEMENT

Disclosure Statement : The authors have no conflicts of Interest to declare.

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