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ASSOCIATION BETWEEN VITAMIN D AND GLAUCOMA: A SYSTEMATIC REVIEW

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ABSTRACT

Background: *Glaucoma is a chronic progressive optic neuropathy that causes irreversible damage. Therefore, early diagnosis and appropriate treatment to control various risk factors associated with glaucoma are important. Risk factors associated with the development of glaucoma have been reported by many researchers and include both ocular and non-ocular (systemic) factors such as myopia, central corneal thickness, disc hemorrhage, and genetic factors.*

The aim: *This study aims to show association vitamin D to glaucoma.*

Methods: *By comparing itself to the standards set 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. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, 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: *In the PubMed database, the results of our search brought up 89 articles, whereas the results of our search on SagePub brought up 98 articles. The results of the search conducted for the last year of 2013 yielded a total 13 articles for PubMed and 26 articles for SagePub. The result from title screening, a total 2 articles for PubMed and 18 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.*

Conclusion: *Decreased serum 25-OHD concentration was associated with the presence but not the severity of POAG. It was suggested that Vitamin D deficiency should be considered a potential risk factor for the development of open-angle glaucoma.*

Keyword: *Glaucoma, Serum 25-hydroxyvitamin D, 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. It is the second worldwide leading cause of blindness. Glaucoma prevalence is variable among different regions worldwide, due to many factors including age, gender, and ethnicity. 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%). 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. Thus, there is a need for population-based studies in KSA for future intervention.[1]

Vitamin D has become a major interest area of medical researchers. Vitamin D is an important secosteroid hormone that plays a role in the signalling pathways related to bone and mineral metabolism, cellular proliferation, immune modulation and the oxidative-stress system. In general, 25-hydroxyvitamin D (25(OH)D) is accepted as the most reliable biomarker for assessing individual vitamin D status. Based on the results of serum 25(OH)D measurements in large population-based studies, it is seen that vitamin D deficiency may be associated with neurodegenerative effects on the central nervous system. Several biological experiments have suggested that vitamin D regulates the functions of neuroprotection in the central nervous system, including in the optic nerve. Moreover, vitamin D status can also affect chronic metabolic diseases, including diabetes, hypertension and dyslipidaemia, which are considered as the important metabolic risk factors of elevated IOP and reduced ocular blood flow. Therefore, it can be hypothesized that vitamin D status is associated with the development of chronic optic neuropathy, i.e. OAG. However, until now, little is known concerning the epidemiological association of vitamin D status with OAG.[2]

Serum 25-OH vitamin D levels are associated with glaucoma. In a study on a South Korean population, participants with low serum 25-OH vitamin D levels were found to be at a significantly elevated risk of open-angle glaucoma (OAG). More recently, in a French case-control study, POAG cases had a lower mean serum 25-OH vitamin D concentration than controls did, as well as a greater prevalence of vitamin D insufficiency. Past findings have also revealed associations between vitamin D levels and various other ocular conditions. Serum 25-OH vitamin D deficiency was associated with a reduced ganglion cell complex in a cohort of older Caucasians. Moreover, a lower serum 25-OH vitamin D concentration was associated with a high risk of myopia in a population of young adults in Australia. In addition, a poorer quality of overall visual acuity was associated with vitamin D insufficiency in older adults. Although the prevalence of glaucoma has been observed to be high in patients of African descent (AD), information is not available on the relationship between serum vitamin D levels and POAG in this population.[3]

The association between Vitamin D3 and ocular fibrosis pathways, with the aim of assessing its viability as a novel therapeutic in the treatment of POAG. It represents a promising agent in reduction of ECM deposition in the TM through its modulation of the TGFβ signaling pathway associated with the development of a fibrotic response associated with POAG. Vitamin D3 has been shown to antagonize TGFß; signaling and promote antifibrotic change within myofibroblastic-type cells, akin to the TMC of patients with POAG. Further research on the implications of reducing ECM deposition in animal models emulating POAG is needed to draw firm conclusions on the effectiveness of Vitamin D3 in attenuating these changes and lowering IOP.[4]

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 of association vitamin D to glaucoma. It is possible to accomplish this by researching or investigating association vitamin D to 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 association vitamin D to 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 2013, 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 " association vitamin D to glaucoma." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *((*"Vitamin D*"[MeSH Subheading] OR "* Vitamin D and glaucoma *"[All Fields] OR "*Effects of vitamin D for eye' *[All Fields]) AND ("Glaucoma"[All Fields]*

OR " Mechanism of glaucoma *"[All Fields]) AND ("*Effects of vitamin D in glaucoma*"[All Fields]) OR ("*Glaucoma mechanism and vitamin D" *[All Fields]))* used in searching the literature.

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 can't have been seen anywhere else.

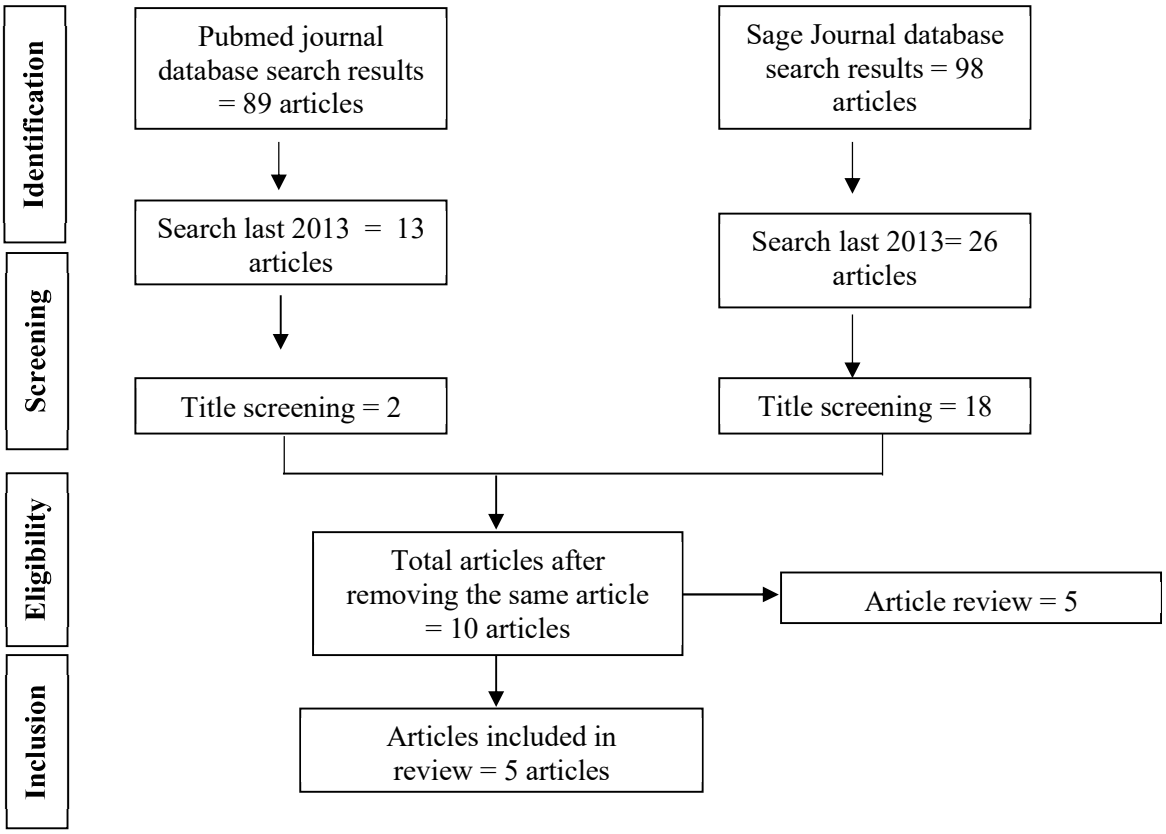

Figure 1. Article search flowchart

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.

RESULT

In the PubMed database, the results of our search brought up 89 articles, whereas the results of our search on SagePub brought up 98 articles. The results of the search conducted for the last year of 2013 yielded a total 13 articles for PubMed

and 26 articles for SagePub. The result from title screening, a total 2 articles for PubMed and 18 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.

Kim, HT *et al* (2016)[5] showed lower serum 25(OH)D level was significantly associated with an elevated risk of glaucoma in women compared to those with higher serum 25(OH)D. Our results suggest that vitamin D status independently affects the pathophysiology of glaucoma in women. We cannot explain the exact mechanism; however, considering both the results of previous reports and the present study, vitamin D influences the pathophysiology of glaucoma as a secondary aggravating factor rather than a primary cause. With the presence of a primary factor, a low vitamin D level might render the optic nerve or its environment more vulnerable to glaucomatous insult. Our study helps to elucidate the risk factors of glaucoma and to disclose the mechanisms underlying the influence of vitamin D on the development of glaucoma.

Lee, T *et al (*2022)[6] showed mean IOP was significantly associated with rates of OCT change, we were not able to find a statistically significant association between mean IOP and rates of SAP MD loss. We believe that the explanation is likely related to the fact that rates of change in SAP may be confounded by the subjective nature of perimetry, as well as by nonlinearities in translating retinal ganglion cell (RGC) loss to visual sensitivity thresholds. Despite this, the lack of association between mean IOP and rates of SAP MD loss is a limitation of our paper and may affect the generalizability of our findings. The study not able to find a statistically significant association between serum vitamin D levels and rates of functional or structural loss in glaucoma. Our findings suggest that serum vitamin D level may not be a useful modifiable factor influencing clinical outcomes in the disease.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Kim, HT *et al*., 2016[5]	Korea	A retrospective, cross-sectional study	169,208 subjects	Of the 169,208 subjects older than 20 years, 123,331 were eligible for the study. There was no difference in the prevalence of glaucoma according to quintile of serum 25(OH)D level based on sex ($p = 0.412$ for males, $p = 0.169$ for females). According to the multivariable-adjusted logistic analysis, the odds ratio of glaucoma for the fourth quintile was significantly lower than that of the first quintile in females (odds ratio, 0.713; 95% confidence interval, 0.520 to 0.979).
Lee, T *et al*., 2022[6]	United Kingdom	A retrospective cohort study	826 eyes	Patients had an average of 3.4 ± 1.7 SAP tests, 4.8 ± 1.9 SD OCT tests, and 2.3 ± 1.9 vitamin D measurements. Average serum vitamin D level was 33.9 ± 13.2 ng/mL. Mean rates of MD and RNFL change were −0.03 ± 0.08 dB/year and −0.68 ± 0.64 µm/year, respectively. After controlling for confounding factors, there was no statistically significant association between mean vitamin D level and rates of MD (β = 0.038, 95% CI: [−0.006, 0.082], p = 0.09) or RNFL loss over time (β = −0.018, 95% CI: [−0.092, 0.055], p = 0.62).
Abass, IA *et al*., 2023[7]	Iraq	A cross-sectional study	61 participants	serum Vitamin D3 levels were 15% significantly lower in the patient's cohort with open-angle glaucoma as compared to the healthy participants ($P <$ 0.05). Among those, 63% of

				type 2 diabetic participants had significantly low levels of Vitamin D3 ($P < 0.01$). There was also a significant 70% reduction in serum Vitamin D3 levels among the hypertensive participants, ($P < 0.001$).
Lee, JH *et al*., 2023[8]	Korea	A retrospective, cross-sectional study	15338 subjects	The cubic spline curve revealed an inverse dose-dependent association between serum 25(OH)D level and EIOP. Using multiple logistic regression analysis, the fully adjusted odds ratio (OR) with 95% confidence interval (CI) for the EIOP of the serum 25(OH)D per increment was 0.97 (0.96–0.990). The fully adjusted ORs (95% CIs) for the EIOP of the 25(OH)D insufficiency and 25(OH)D sufficiency groups, compared to 25(OH)D deficiency group, were 0.72 (0.56–0.92) and 0.51 (0.34–0.78), respectively. The relationship remained significant in male and young age subgroups. In conclusion, the clinical assessment of intraocular pressure may prove helpful when treating patients with 25(OH)D deficiency, which may be a preventive strategy against the development of glaucoma.
Lv, Y *et al*., 2016[9]	China	A case–control study	144 participants	Serum levels of 1a, 25-Dihydroxyvitamin in primary open-angle glaucoma patients were lower than in 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, while other polymorphisms did not show any significant differences.

Abass, IA *et al* (2023)[7] showed lower serum levels of Vitamin D were significantly associated with an elevated risk of glaucoma in our patients. The females were more significantly affected as compared to males. Our data suggest that Vitamin D status independently affects the pathophysiology of glaucoma in women. Although the exact mechanism is not very clear, considering both the results of previous reports and the present study, Vitamin D influences the pathophysiology of glaucoma as a secondary aggravating factor rather than a primary cause. With the presence of a primary factor, a low Vitamin D level might render the optic nerve or its environment more vulnerable to glaucomatous insult.

Lee, JH *et al* (2023)[8] showed Serum 25(OH)D levels are inversely associated with EIOP. In particular, people with 25(OH)D deficiency are at a higher risk of EIOP than people with 25(OH)D insufficiency or 25(OH)D sufficiency. Thus, it may be helpful for clinicians to check intraocular pressure when treating patients with 25(OH)D deficiency, as this may be a preventive strategy against glaucoma. More randomized controlled trials should be performed to confirm the causal relationship between 25(OH)D levels and glaucoma development, with consideration of the angle structure. Experimental studies are warranted to identify the association between 25(OH)D and intraocular pressure.

Lv, Y *et al* (2016)[9] showed Vitamin D deficiency, the BsmI 'B'allele and the TaqI 't' allele point to their direct roles in POAG development. However, the causes of 1a, 25-Dihydroxyvitamin D3 deficiency, the changes in the structure and function of VDR and the frequency of allele carriers of polymorphisms of VDR require further study. The possibility of administering vitamin D3 to POAG patients who have low levels of 1a, 25-Dihydroxyvitamin D3, and the question of whether 1a, 25-Dihydroxyvitamin D3 affects intraocular pressure should be further investigated.

DISCUSSION

Glaucoma is the leading cause of irreversible blindness in the world. The disease can be characterized as a progressive optic neuropathy, where gradual visual field loss eventually leads to blindness. Primary open-angle glaucoma (POAG) is the most common type of glaucoma; it is typically asymptomatic at the early stages, and it is often not diagnosed until irreversible loss of the visual field transpires. Well-known risk factors are elevated intraocular pressure (IOP), advanced age, positive family history, and African ancestry. The prevalence of glaucoma has been reported to be higher in black compared with white and mixed-race populations. Similarly, the mean IOP was reported to be highest in black compared with mixed-race or white patients. Currently, no reliable methods or biomarkers for the early detection of glaucoma are available.[3]

Vitamin D has diverse functions in maintaining human health, including regulating gene expression, immune system, inflammation, cell proliferation and differentiation, apoptosis, and angiogenesis. Vitamin D_3, or cholecalciferol, is produced from its precursor, 7-dehydrocholesterol, in the epidermal layer of skin under exposure to sunlight, or is obtained from the diet. It is metabolized in the liver and kidneys to its biologically active forms, 25-hydroxyvitamin D ($25(OH)D_3$) and 1,25-dihydroxyvitamin D ($1,25(OH)_2D_3$), respectively. The latter is also known as potent steroid hormone calcitriol. Reduced sun exposure will lead to vitamin D deficiency. Low vitamin D levels have been associated with many diseases, including cardiovascular diseases, hypertension, diabetes mellitus, and cancers.[10]

Vitamin D is synthesized and activated in three steps. Cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) are the two major biologically inert precursors of vitamin D. For the former, 7-dehydrocholesterol in the skin produces previtamin D3 under exposure to ultraviolet B radiation (UVB, λ = 290–315 nm), which then thermally isomerizes to Vitamin D_3 in the skin; in contrast, vitamin D_2 is derived from plants and obtained from the diet. After its production, vitamin D_3 attaches to vitamin D-binding protein (DBP) in the liver, where it is activated to produce $25(OH)D_3$, the primary circulating form of vitamin D, by 25-hydroxylases, CYP2R1 and CYP27A1. Then, $25(OH)D_3$ is converted to $1,25(OH)_2D_3$, the active form of vitamin D, by 1α-hydroxylase, CYP27B1. In contrast, vitamin D_2 is derived from plants and obtained from the diet. CYP27A1 does not hydroxylate vitamin D_2 at the 25 positions. Lastly, vitamin D metabolite levels are downregulated by CYP24A1, which catalyzes the 24-hydroxylation of both $25(OH)D_3$ and $1,25(OH)_2D_3$. The genetic variation in the metabolic enzyme would affect the regulation of vitamin D levels.[10]

Recent studies have revealed that vitamin D deficiency can lead to various ocular diseases. Those with low 25-hydroxyvitamin D levels have been associated with the risk of diseases involving dry eyes, diabetic retinopathy, myopia, age-related macular degeneration (AMD), whereas higher levels have been linked with decreased frequency of diseases. Also, vitamin D treatment has been experimentally shown to improve the conditions of those with diseases such as retinoblastoma, choroidal melanoma, retinal aging, ischemic retinopathy, diabetic retinopathy, autoimmune uveitis, corneal damage, and glaucoma.[11]

Glaucoma is a leading cause of irreversible blindness worldwide, contributing to approximately 10% of cases of legal blindness registered in the United States. The core event in glaucoma is irreversible damage of retinal ganglion cell axons, which carry visual information from the eye to the brain, due to elevated intraocular pressure (IOP). Depending on the mechanism of increasing IOP, glaucoma could be classified into two categories: angle-closure glaucoma (ACG) or open-angle glaucoma (OAG). Unlike ACG, which has a narrow iridocorneal angle, OAG is characterized by increased resistance in the trabecular meshwork (TM), which causes an elevation of IOP. Several studies have suggested that changes in the concentration of various molecules in aqueous humor, such as vitamin C, hyaluronic acid, transforming growth factor β (TGF-β)[5], and endothelin-1, increase TM resistance.[12]

Vitamin D does not exhibit biological activity until two-step hydroxylation occurs. Following the hydroxylation of vitamin D into 25-hydroxy vitamin D [25(OH)D] in the liver, the vitamin D metabolite is transported to kidneys where it is converted to 1α, 25-dihydroxyvitamin D [1α, 25(OH)2D], which is an active form of vitamin D[7,8]. The vitamin D status is usually evaluated by measuring 25(OH)D concentrations. Its deficiency affects bone and mineral metabolism; however, recent studies have reported that vitamin D insufficiency is associated with various systemic diseases. Adequate vitamin D intake can prevent diseases, such as myocardial infarction, stroke, diabetes mellitus types 1 and 2, infectious or chronic respiratory diseases, and autoimmune diseases. Furthermore, the serum concentrations of vitamin D has been linked to the prevalence or occurrence of eye disorders, such as diabetic retinopathy, age-related macular degeneration, myopia, and dry eye syndrome. In particular, several studies have demonstrated that the serum concentration of vitamin D is associated with OAG.[12]

CONCLUSION

Decreased serum 25-OHD concentration was associated with the presence but not the severity of POAG. It was suggested that Vitamin D deficiency should be considered a potential risk factor for the development of open-angle glaucoma. 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.

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