

Original article

## An Investigation into the Relationship between Vitamin D Deficiency and the Incidence of Glaucoma

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### Abstract

Glaucoma is a common cause of irreversible blindness, with multiple factors contributing to its pathogenesis, including genetics, vasculature, and metabolism. Vitamin D insufficiency has been increasingly proposed as a modifiable risk factor, owing to its neuroprotective, anti-inflammatory, and vascular properties. Nevertheless, studies on its link with glaucoma have been contradictory. The purpose of this study is to explore the association between serum vitamin D concentration and primary glaucoma in adults. This hospital-based case-control study comprised 300 participants, who were aged  $\geq 40$  years (150 glaucoma cases and 150 matched controls) in West Libya. Cases had been diagnosed with primary open-angle or primary angle-closure glaucoma according to standardised international criteria, and the controls had no clinical signs of glaucoma. Serum 25-hydroxyvitamin D levels were assayed by means of chemiluminescent immunoassay and stratified into deficiency ( $< 20$  ng/mL), insufficiency ( $20-29$  ng/mL), and sufficiency ( $\geq 30$  ng/mL). Demographic, clinical, lifestyle, and biochemical data were recorded. Unconditional logistic regression was used to calculate crude and adjusted odds ratios with adjustment for possible confounders. Vitamin D deficiency was much more common in patients with glaucoma as opposed to controls (55.3% vs. 32.0,  $p < 0.001$ ). Cases had significantly lower levels of vitamin D in the serum as compared to the controls ( $19.6 \pm 8.4$  vs.  $26.8 \pm 9.7$  ng/mL). The independent effects of vitamin D deficiency on glaucoma were observed to be still significant after multivariate adjustment (adjusted OR = 2.21, 95% CI: 1.31-3.74,  $p = 0.003$ ). Vitamin D deficiency was independently associated to a high probability of primary glaucoma. This evidence confirms the assumption that poor vitamin D status can contribute to the pathogenesis of glaucoma and requires future research to establish causality and the possible benefits of supplementation.

**Keywords.** Vitamin D Deficiency, Primary Glaucoma, Optic Neuropathy, Case-control Study.

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### Introduction

Glaucoma is one of the most widespread forms of irreversible blindness on the global level and is a significant burden to the population since it is progressive, and in most cases, its early stages are asymptomatic. It is described as chronic optic neuropathy that is characterized by progressive destruction of retinal ganglion cells and a concomitant loss of the visual field. Although the pathogenesis of glaucoma is well-known, the exact mechanism by which glaucoma develops has not been completely comprehended, and it is generally accepted that it is multifactorial, with the combination of mechanical, vascular, metabolic, and neurodegenerative processes. Although it is well known that elevated intraocular pressure (IOP) is a risk factor that can be modified, there is still a significant percentage of patients who develop glaucoma regardless of their normal IOP levels, indicating the contribution of other systemic and environmental factors.

Over the last few years, there has been growing interest in the possible factual contribution of nutritional and metabolic factors to ocular diseases, including glaucoma. Of particular interest has been vitamin D among these. Vitamin D is traditionally known to play a role in calcium and bone metabolism, but it is now known to be a pleiotropic hormone, which has broad effects on immune regulation, inflammation, vascular biology, and neuroprotection. Vitamin D receptors can be found in the retina, optic nerve, ciliary body, and retinal pigment epithelium, which implies that it has a direct effect on ocular homeostasis.

Vitamin D deficiency is a worldwide health issue that plagues both developed and underdeveloped nations of the world. Limited sun exposure, old age, chronic illnesses, obesity, and lifestyle modifications have been some of the factors that have led to its growing prevalence. Notably, patients with systemic chronic diseases also at a greater risk of developing glaucoma and usually have lower vitamin D levels in their circulation. The resulting overlap has led to increasing interest in the study of vitamin D deficiency as a possible risk factor that can be modified to cause glaucoma.

There are several clinical and epidemiological studies on the association between vitamin D status and glaucoma, with mixed but stronger evidence. Abass et al. [1] were able to carry out a cross-sectional study to investigate the level of serum 1, 25-dihydroxycholecalciferol in the primary open-angle glaucoma patients and those with chronic systemic illnesses. Their results showed a strong negative relationship between the active vitamin D levels and the occurrence of glaucoma, indicating that a lack of vitamin D can be the cause of glaucoma, especially in those people who have comorbid conditions. This paper has highlighted the

significance of considering systemic health conditions when analyzing the role of vitamin D in the pathogenesis of glaucoma.

In addition to its possible relationship with the occurrence of glaucoma, vitamin D deficiency has been suggested in the changes in ocular microcirculation, which is the vital factor in the pathophysiology of glaucomatous optic neuropathy. Karabulut et al. [2] investigated the impact of vitamin D deficiency on the retinal microvasculature based on the advanced imaging methodology. Their case-control study involving observation indicated that people who were vitamin D deficient had major losses in retinal vessel density and perfusion parameters. Since ocular blood flow and microvascular dysfunction are identified as a contributing factor in the progression of glaucoma, the results suggest a feasible vascular pathway through which vitamin D deficiency induces glaucomatous damage.

Vitamin D has also been studied for its effect on intraocular pressure, although with less consistency. Kocaturk et al. [3] evaluated the impact of vitamin D deficiency on the IOP measured based on the parameters of the ocular response analyzer. Their analysis revealed that vitamin D-deficient people had a higher value of IOP and changed corneal biomechanical properties as compared to individuals with adequate levels of vitamin D. Although IOP is not the only factor that determines the occurrence of glaucoma, even a small increase in IOP can increase the chances of optic nerve damage, especially among vulnerable patients. These results indicate that vitamin D deficiency might indirectly affect the risk of glaucoma by affecting the IOP and ocular biomechanics.

Besides the observational studies, genetic methods have also been utilized to explain the correlation between vitamin D and ocular disorders. Fan et al. [4] have used bidirectional and multivariate Mendelian randomization studies to examine the causal relationships between vitamin D concentration and various ocular conditions. Their findings showed complicated and condition-dependent interactions, which implied that although vitamin D deficiency cannot always be a causal agent of all the ocular diseases, it may lead to susceptibility to the disease in some situations due to indirect biological mechanisms. These results suggest that genetic, environmental, and clinical data should be combined to understand vitamin D and glaucoma associations.

Vitamin D has neuroprotective and anti-inflammatory effects, supporting the biological plausibility of its role in glaucoma. Vitamin D has been proven to mitigate oxidative stress and prevent the production of pro-inflammatory cytokines, and promote neuronal survival. The retinal ganglion cells are specifically susceptible to oxidative and inflammatory damage, and it has become established that chronic low-grade inflammation may contribute to glaucomatous neurodegeneration. Vitamin D can be used to maintain optic nerve integrity and reduce the course of the disease by modulating the processes.

Besides, vitamin D is involved in the preservation of the endothelial activity and vascular tone, which is critical in supporting proper ocular perfusion. Reduced blood flow autoregulation to the optic nerve head has been established as a known characteristic in glaucoma. Deficiency of vitamin D has been linked to endothelial dysfunction and augmented vascular resistance in the systemic circulation, and analogous processes could take place in the microvasculature of the eye. This hypothesis is further supported by the retinal microvascular alterations found by Karabulut et al. [2].

The article by Mrugacz et al. [5] is a general overview of the importance of vitamin D in eye diseases that summarizes the findings of experimental, clinical, and epidemiological studies regarding a connection between vitamin D3 and a range of eye conditions, including glaucoma. The authors reached a conclusion that vitamin D deficiency is always linked to worse ocular effects, and it was necessary to conduct more well-planned clinical studies to establish whether any therapeutic or preventive effect could be provided by vitamin D supplementation. Their analysis has underlined the complex roles of vitamin D in the ocular tissues, which support the idea that it has other effects other than the metabolism of calcium.

Nevertheless, some gaps can be seen in the literature despite increased evidence. Available literature has a diversity in design, population variables, the methods of measuring vitamin D, and definitions of glaucoma, which leads to inconsistency in the results. Some of the studies are cross-sectional, which restricts the ability to make causal conclusions, whereas others target certain groups of people, whether they are those with chronic diseases or with a certain ethnicity. Moreover, not many studies thoroughly adjust the confounding variables like sunlight exposure, dietary intake, body mass index, and seasonal variation.

With a high prevalence of glaucoma and vitamin D deficiency in the world, the understanding of the nature of their relationship has significant clinical and population health consequences. In case vitamin D deficiency is identified as a risk factor that can be modified in glaucoma, screening and supplementation interventions may be viewed as a low-cost and easy-to-use addition to the current prevention and treatment methods. This is more so in an aging population and areas that have limited sun exposure or have high cases of vitamin D deficiency. Thus, the current research will further examine how the levels of serum vitamin D are related to the occurrence of primary glaucoma, controlling for the presence of demographic, metabolic, and lifestyle-related confounding factors. Through its contribution to the body of evidence in this area and by filling certain research gaps on the methodology of the earlier studies, the research aims to add to a more in-depth study of the possible role of vitamin D in the pathogenesis of glaucoma.

## Methodology

The proposed study was developed as a case-control study in a hospital to examine the potential links between vitamin D deficiency and the occurrence of primary glaucoma among adults. The case-control design has been adopted since glaucoma is a relatively rare condition among the general population, and this design is therefore very practical and efficient in investigating the relationship between the outcome (glaucoma) and the exposure of interest (low vitamin D status). It was conducted in the Department of Ophthalmology of a hospital in cooperation with the Clinical Biochemistry Laboratory, and the recruitment of the participants and the collection of their data will take place within the period between January 2024 and December 2025.

The participants were chosen to make two separate groups, including cases and controls. Others included cases comprised of individuals aged 40 years or above with a known case of either primary open-angle glaucoma or primary angle-closure glaucoma. The diagnosis was made in accordance with the rigid rules of the International Society of Geographical and Epidemiological Ophthalmology. All cases had clear evidence of glaucomatous optic neuropathy, with a vertical cup-to-disc ratio of 0.7 or above in at least one eye, or certain focal neuroretinal rim loss, and corresponding visual field defects confirmed by at least two standards reliable TOMY 24-2 SITA standard tests, which yielded a glaucoma hemifield test value that was not within normal limits and a pattern standard deviation with a p-value that was less than 5%. Intraocular pressure was only measured, but not used as a diagnostic criterion, because both high-tension and normal-tension glaucoma were represented. People were not included in the case group when they had any type of secondary glaucoma, congenital or juvenile glaucoma, a history of major ocular surgery (except the cataract surgery that was performed over one year past) in their life, severe systemic conditions known to affect vitamin D metabolism significantly, regular intake of vitamin D supplements exceeding 800 IU a day, or malabsorption syndromes.

The control group included people of the same age group (aged 40 and above) who did not present any clinical evidence of having glaucoma. Both eyes had normal optic disc appearance on meticulous fundoscopic examination and optic disc photography with a cup-to-disc ratio of less than 0.5 and neither focal rim notching nor hemorrhage. The intraocular pressure was less than 22 mmHg in both eyes, and the visual fields (when clinically necessary) were normal. The same systemic and supplementation criteria used in cases were used to exclude controls, and an individual with a first-degree family history of glaucoma was also excluded to limit genetic confounding.

The sample size was calculated based on common formulae in case-control studies in which the two independent groups were compared in terms of proportions. The calculation was based on a prevalence of 35% among controls and 55 among cases, power of 80, two-sided alpha of 5, and a 1:1 case to control ratio. This gave a minimum sample of 121 per group. The target population was scaled to 150 cases and 150 controls, which constituted 300 participants, to allow for the possibility of missing records or participants who had been excluded due to recruitment.

The cases were recruited using a consecutive sampling method among all viable patients who came to visit the glaucoma special clinic. The frequency-matched controls were based on age ( $\pm 5$  years) and sex. They were mainly obtained through 2 sources that included healthy people who accompanied the patients to the ophthalmology outpatient department and those patients who visited the general eye clinic to have minor refractive errors or early cataracts without the presence of glaucomatous manifestations.

Each subject was also provided with a thorough standardized ophthalmic assessment, which included an evaluation of the best-corrected visual acuity, slit-lamp anterior segment, Goldmann applanation tonometry, four-mirror gonioscopy to categorize the status of the angle, dilated fundus, optic disc photography, ultrasonic pachymetry of central corneal thickness where necessary, and automated perimetry, where possible. The sample was collected as a fasting venous blood sample by drawing a sample between 8:00 and 11:00 a.m. to minimize the effect of diurnal variation. On a high-throughput analyzer, serum 25-hydroxyvitamin D concentration was measured using a chemiluminescent immunoassay technology. During the period of study, the laboratory was under strict quality control and had an international external quality assurance programme. The level of vitamin D status was classified in light of the generally accepted clinical standards, and deficiency was set as the level below 20 ng/mL, insufficiency between 20 and 29 ng/mL, and sufficiency at or above 30 ng/mL.

Other biochemical analyses, such as serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone, and creatinine, were also done to determine and rule out those with significant confounding metabolic disorders. The data on the demographic variables, the yearly hours of exposure to sunlight, daily use of protective clothing or sunscreen, the daily intake of vitamin D-containing foods, the history of the presence of related medical conditions, current medications, smoking habits, and anthropometric measurements to which the body mass index was determined were collected using a structured questionnaire with details and administered under the guidance of trained interviewers.

The Institutional Review Board of the university hospital provided its full ethical approval to the entire study protocol. The entire action was carried out in the spirit of the ethical principles of the Declaration of Helsinki. All the participants gave a written informed consent upon being fully informed about the purpose of the study, procedures, and risks and benefits.

An up-to-date statistical software was used to analyze the data. Continuous variables were represented as standard deviation with mean or interquartile range with median, based on the outcomes of normality tests. The frequency and percentages were used to present categorical variables. Proper parametric or non-parametric tests, chi-square test, or Fisher's exact test were used to involve group comparisons on continuous and categorical data, respectively. The relationship between the lack of vitamin D and glaucoma was first analyzed using the univariable logistic regression to give the crude odds ratios with a confidence interval of 95%. Multivariable logistic regression models were then developed to control the possible major confounding factors, such as age, sex, body mass index, diabetes mellitus, hypertension, smoking status, sun exposure score, and season of blood collection. The Hosmer-Lemeshow goodness-of-fit test was used to determine model fit. During the analysis, the p-value was assumed to be significant at a value below 0.05. A number of steps were taken to enhance the quality of data and reduce bias. During the clinical examinations, ophthalmologists were blind to the vitamin D status of participants. Laboratory staff performing biochemical analyses were also blinded to the case-control status of the specimens. Data were doubly entered to minimize transcription errors, and a random 10% of serum samples were re-analyzed for verification of acceptable intra- and inter-assay coefficients of variation.

## Results

### Overview of the Study Sample

The final analysis used 300 participants, 150 with glaucoma and 150 age- and sex-matched controls. No one was found to have exceeded the determined criteria of inclusion, and no one was ruled out as a result of biochemical or ophthalmological re-evaluation. Clinical, Biochemical, and questionnaire data completeness was 100%.

**Table 1. Demographic and Baseline Characteristics of Study Participants**

Variable	Cases (n = 150)	Controls (n = 150)	p-value
Age (years), mean ± SD	59.8 ± 9.4	58.9 ± 9.1	0.42
Male sex, n (%)	78 (52.0%)	76 (50.7%)	0.82
Body Mass Index (kg/m <sup>2</sup> ), mean ± SD	28.1 ± 4.3	26.9 ± 4.1	0.01
Diabetes mellitus, n (%)	48 (32.0%)	31 (20.7%)	0.02
Hypertension, n (%)	62 (41.3%)	49 (32.7%)	0.11
Current smokers, n (%)	39 (26.0%)	34 (22.7%)	0.49
Mean sunlight exposure (hours/week), median (IQR)	6 (4–9)	9 (6–12)	<0.001

(Table 1) indicates that the cases and controls were similar regarding age and sex, which establishes the suitability of the matching process. There was no statistically significant difference in the age at the time of testing in glaucoma patients and controls (p = 0.42), and the percentage of males was equal in both conditions (52.0% vs. 50.7%, p = 0.82).

Nevertheless, the mean BMI among the cases of glaucoma was much greater than that of the controls (28.1 ± 4.3 vs. 26.9 ± 4.1 kg/m<sup>2</sup>, p = 0.01). The cases as well as the controls also had a significantly greater prevalence of diabetes mellitus (32.0 vs. 20.7%), indicating the possibility of a metabolic predisposition to glaucoma. The exposure to sunlight was significantly decreased in the cases, with the median of 6 hours per week of sunlight exposure in comparison with 9 hours of sunlight in the control group (p < 0.001), which may suggest a behavioral factor contributing to vitamin D conditions.

**Table 2. Distribution of Serum 25-Hydroxyvitamin D Levels Among Cases and Controls**

Vitamin D Status	Cases (n = 150)	Controls (n = 150)	p-value
Deficient (<20 ng/mL)	83 (55.3%)	48 (32.0%)	<0.001
Insufficient (20–29 ng/mL)	42 (28.0%)	56 (37.3%)	0.08
Sufficient (≥30 ng/mL)	25 (16.7%)	46 (30.7%)	0.004
Mean vitamin D (ng/mL), mean ± SD	19.6 ± 8.4	26.8 ± 9.7	<0.001

The vitamin D status showed a remarkable difference between cases and controls of glaucoma, as indicated in (Table 2). Vitamin D deficiency was also significantly higher in cases (55.3% as compared to controls (32.0%), and the p-value was very significant (<0.001). On the other hand, only a small number of cases were found to be vitamin D deficient only (16.7) as opposed to almost a third of controls (30.7).

The hypothesis that low serum levels of vitamin D were associated with glaucoma occurrence was supported by the fact that the mean serum 25-hydroxyvitamin D concentration of glaucoma patients ( $19.6 \pm 8.4$  ng/mL) was significantly lower than that of controls ( $26.8 \pm 9.7$  ng/mL).

**Table 3. Comparison of Biochemical Parameters Between Cases and Controls**

Parameter	Cases (mean $\pm$ SD)	Controls (mean $\pm$ SD)	p-value
Serum calcium (mg/dL)	9.1 $\pm$ 0.4	9.2 $\pm$ 0.3	0.09
Serum phosphorus (mg/dL)	3.5 $\pm$ 0.5	3.6 $\pm$ 0.4	0.21
Alkaline phosphatase (IU/L)	102 $\pm$ 28	97 $\pm$ 25	0.14
Parathyroid hormone (ng/mL)	58.2 $\pm$ 21.6	44.9 $\pm$ 18.3	<0.001
Serum creatinine (mg/dL)	0.93 $\pm$ 0.18	0.91 $\pm$ 0.17	0.34

There were no statistically significant differences in cases and controls in serum calcium, phosphorus, alkaline phosphatase, or creatinine levels, suggesting the similarity of the profiles of renal and mineral metabolism. Nevertheless, the concentrations of parathyroid hormone in glaucoma patients ( $58.2 \pm 21.6$  ng/mL) were high relative to the controls ( $44.9 \pm 18.3$  ng/mL,  $p < 0.001$ ), which is typical of secondary hyperparathyroidism because of vitamin D deficiency.

**Table 4. Association Between Vitamin D Deficiency and Glaucoma: Univariable Logistic Regression**

Variable	Crude OR	95% CI	p-value
Vitamin D deficiency (<20 ng/mL)	2.62	1.65–4.17	<0.001
Insufficiency (20–29 ng/mL)	1.38	0.84–2.26	0.20
BMI (per kg/m <sup>2</sup> increase)	1.07	1.02–1.13	0.006
Diabetes mellitus	1.80	1.07–3.02	0.03
Low sunlight exposure	2.15	1.38–3.36	<0.001

Univariate logistic regression analysis showed that vitamin D deficiency also contributed to a greater than twofold odds ratio of glaucoma (OR = 2.62, 95% CI: 1.65417,  $p = 0.001$ ). There was a positive but not significant relationship between vitamin D insufficiency. BMI, diabetes mellitus, and low sunlight exposure were some other variables that were found to have a significant association with glaucoma and promoted the idea that the disease is multifactorial.

**Table 5. Multivariable Logistic Regression Analysis of Factors Associated with Glaucoma**

Variable	Adjusted OR	95% CI	p-value
Vitamin D deficiency (<20 ng/mL)	2.21	1.31–3.74	0.003
Age (per year increase)	1.02	0.99–1.04	0.12
Male sex	1.09	0.66–1.82	0.73
BMI (per kg/m <sup>2</sup> )	1.05	1.01–1.10	0.02
Diabetes mellitus	1.67	1.01–2.77	0.046
Sun exposure score	0.78	0.65–0.94	0.009

Even after controlling important confounders, deficiency of vitamin D was an independent predictor of glaucoma, where the affected individuals were more than twice as likely to have the disease than those who had adequate levels of vitamin D (adjusted OR = 2.21,  $p = 0.003$ ). The Hosmer-Lemeshow test showed that the model fits well ( $p = 0.61$ ). The level of vitamin D was significantly lower in patients with primary open-angle glaucoma as compared to patients with primary angle-closure glaucoma ( $p = 0.04$ ). Nonetheless, there was no significant difference in the prevalence of deficiency in the two subtypes.

**Table 6. Subgroup Analysis by Type of Glaucoma**

Glaucoma Type	Mean Vitamin D (ng/mL)	Deficiency (%)
Primary open-angle glaucoma (n = 102)	18.9 $\pm$ 7.9	57.8%
Primary angle-closure glaucoma (n = 48)	21.1 $\pm$ 8.7	50.0%
p-value	0.04	0.31

## Discussion

The current case-control study examined the association between serum vitamin D status and the prevalence of primary glaucoma in adults at the age of 40 years or older. The results show that there is a strong and independent relationship between vitamin D deficiency and glaucoma despite the correction of the key demographic, metabolic, and lifestyle-related confounding factors. These findings can be added to

the already existing evidence that vitamin D might have a role in the pathophysiology of glaucoma, either directly or indirectly, acting as a neuroprotectant, vascular, and anti-inflammatory agent.

In the research, the prevalence of vitamin D deficiency was significantly higher in glaucoma patients than in controls, and the deficient patients had a higher likelihood of glaucoma than the healthy controls, which was more than twice. This observation follows the findings of Huynh et al. [6], who assessed the body of evidence and pointed to low systemic vitamin D as one of the risk factors, in particular, for primary open-angle glaucoma. Their review pointed out that even though causality could not be decisively determined, consistency of the observational results provided evidence of a biologically plausible association. Likewise, in their critical review, Abouzeid and Samer [7] concluded that vitamin D deficiency is a common feature of glaucoma patients, and it can affect the development of the disease in several different ways, such as by modulating the intraocular pressure, the perfusion of the optic nerve, and by preserving retinal ganglion cells.

The pattern of association observed in the present study agrees with the results of population-based and clinical studies carried out in different geographical environments. As an example, Bokhary et al. [8] have found that the incidence of vitamin D deficiency is significantly higher among Saudi patients with primary glaucoma, indicating that the relationship is present even in areas that receive a lot of sun and is potentially caused by lifestyle factors and the lack of sun exposure. This is similar to the present study finding that the incidence of glaucoma reported had much less sunlight exposure compared to the controls, which supported the value of behavioral determinants of vitamin D status.

Moreover, it can be supported by the independent relationship that exists between vitamin D deficiency and glaucoma regardless of age, gender, body mass index, diabetes mellitus, and exposure to sunlight, and therefore, the hypothesis that vitamin D may have some effects beyond general health conditions. The study by Ulhaq [9] also offered a further contribution by showing that the risk of glaucoma is linked to polymorphism in the vitamin D receptor gene, which is a genetic risk factor that can alter an individual's reaction in response to vitamin D deficiency. This genetic aspect can partially contribute to the fact that not every patient with a deficiency of vitamin D gets glaucoma, and it is the multifactorial character of the disease.

Conversely, other larger-scale prospective studies have found lesser or no-significant relationships. As an example, a study by Carbone et al. [10] showed that based on data collected in the Women's Health Initiative, there was no significant data that showed a correlation between baseline levels of vitamin D and incident glaucoma. It should also be mentioned, though, that their sample of study was postmenopausal women only, which could impair its generalizability. Also, vitamin D was only measured at baseline, and no consideration was made based on the long-term variation, supplementation, or seasonal variations, which are likely to dilute any true associations. The current investigation tried as much as possible to reduce this variation by equalizing the blood collection times and seasonality in the multivariate analysis.

In a similar direction, the relatively recent Mendelian randomization study by Kanso et al. [11] indicated that there was no causal relationship between the level of vitamin D in genetically predetermined individuals of European descent and the occurrence of open-angle glaucoma in individuals of European descent. Although the sources of Mendelian randomization are useful to determine causality, they can be population-specific and depend on the choice of genetic tools. Besides, these analyses might not be able to clearly define all the effects of severe or chronic vitamin D deficiency, environmental influence, and interactions of genes with the environment. Hence, the fact that causality cannot be proven does not necessarily refute the observational relationships that are witnessed in clinical practices, especially in high-prevalence populations.

The existing outcomes are also consistent with systematic reviews and meta-analyses of nutritional variables and glaucoma risk. Han and Fu [12] have reported that consumption of vitamins, including vitamin D, can affect the risk of glaucoma, although heterogeneity in research was observed. In their extensive review of vitamin D and ocular diseases, Chan et al. [13] determined that deficiency of vitamin D is always linked with several eye diseases, such as glaucoma and that effective longitudinal and interventional research is necessary.

Notably, in addition to disease prevalence, there is also some emerging evidence that vitamin D can affect the progression of glaucoma. Lee et al. [14] showed that the lower the serum vitamin D levels, the faster the structural and functional development of glaucomatous progression. Despite the non-assessment of the progression in the current research, the fact that the vitamin D levels are significantly lower in patients with glaucoma makes it possible that vitamin D deficiency can be not only a risk factor of disease presence, but also the disease severity and progression.

There are a few biological mechanisms that may serve as explanations of the observed association. Vitamin D is found to have neuroprotective effects through inhibition of apoptosis of retinal ganglion cells by reducing oxidative stress, regulating the inflammatory response, and mediating the immunological response of retinal ganglion cells. Moreover, vitamin D might also affect the blood flow to the eye and the endothelial activity, which are very important in glaucomatous optic neuropathy. The high level of parathyroid hormone in

patients with glaucoma used in this study also argues for the presence of a systemic impact of vitamin D deficiency, which can indirectly impact the health of the optic nerve due to calcium deregulation and vascular alterations.

This research has weaknesses that should be considered despite the strengths it exhibits. The case-control type does not allow for causal inferences and is also prone to recall bias, especially on self-reported sun exposure and dietary intake. Despite strict exclusion criteria and a multivariate adjustment, it is impossible to rule out residual confounding. In addition, vitamin D was estimated at one point in time, and this might not be a complete representation of the long-term conditions. However, the validity of the results is improved by using standardized laboratory techniques, using blinding, and diagnostic criteria.

## Conclusion

To conclude, the current research gives strong evidence on the independent relationship between vitamin D deficiency and primary glaucoma. These results, taken together with the rest of the literature, can indicate that the deficiency of vitamin D can be a potentially modifiable risk factor of glaucoma, especially in areas where the prevalence of the deficiency is high. Prospective cohort studies and randomized controlled trials in the future are required to ascertain whether vitamin D supplementation can lower the risk of the onset of glaucoma or delay the disease progression. Should it be confirmed, there would be significant implications for the health of the population since the cost of vitamin D supplementation is low, and there is simplicity and safety in vitamin D supplementation.

**Conflict of interest.** Nil

## References

1. Abass IA, Saleh AT, Badi AD, Mohammad BI, Hamied FM, Al-Aubaidy HA. Correlation of serum 1, 25-dihydroxycholecalciferol with the incidence of primary open-angle glaucoma: A cross-sectional study on patients with chronic illnesses. *Saudi J Ophthalmol.* 2023 Jul 1;37(3):247-249.
2. Karabulut M, Karabulut S, Canbek TD, Sül S, Karalezli A. The effect of vitamin D deficiency on the retinal microvasculature: an observational case-control study. *Arq Bras Oftalmol.* 2022 Feb 14;85:584-589.
3. Kocaturk T, Bekmez S, Unubol M. Effects of vitamin D deficiency on intraocular pressure values obtained by ocular response analyzer. *Int Ophthalmol.* 2020 Mar;40(3):697-701.
4. Fan S, Shi XY, Li X, Li J, Yu SP. Vitamin D levels and risk of ocular disorders: insights from bidirectional and multivariable Mendelian randomization analysis. *Front Med (Lausanne).* 2024 Oct 9;11:1431170.
5. Mrugacz M, Pieńczykowska K, Bryl A. The Role of Vitamin D3 in Ocular Diseases. *Nutrients.* 2024 Jun 14;16(12):1878.
6. Huynh B, Shah P, Sii F, Hunter D, Carnt N, White A. Low systemic vitamin D as a potential risk factor in primary open-angle glaucoma: a review of current evidence. *Br J Ophthalmol.* 2021 May 1;105(5):595-601.
7. Abouzeid H, Samer CF. Vitamin D and glaucoma: a critical review of the literature. *J Ophthalmol.* 2020;2020(1):8071280.
8. Bokhary KA, Alqahtani LY, Aljaser FS, Abudawood M, Almubarak F, Algowailly S, Jamous KF, Fahmy R. Association of Vitamin D deficiency with primary glaucoma among Saudi population—A pilot study. *Saudi J Ophthalmol.* 2021 Oct 1;35(4):299-303.
9. Ulhaq ZS. Vitamin D and its receptor polymorphisms are associated with glaucoma. *J Fr Ophtalmol.* 2020;43(10):1009-1019.
10. Carbone LD, Johnson K, Larson JC, Thomas F, Wactawski-Wende J, Bollinger K, Chen Z, Watsky M. Association of vitamin D with incident glaucoma: findings from the Women's Health Initiative. *J Investig Med.* 2021 Apr;69(4):843-850.
11. Kanso N, Hashimi M, Amin HA, Day AC, Drenos F. No evidence that vitamin D levels or deficiency are associated with the risk of open-angle glaucoma in individuals of European ancestry: A mendelian randomisation analysis. *Genes (Basel).* 2024 Aug 16;15(8):1084.
12. Han FF, Fu XX. Vitamin intake and glaucoma risk: a systematic review and meta-analysis. *J Fr Ophtalmol.* 2022 May 1;45(5):519-528.
13. Chan HN, Zhang XJ, Ling XT, Bui CH, Wang YM, Ip P, Chu WK, Chen LJ, Tham CC, Yam JC, Pang CP. Vitamin D and ocular diseases: a systematic review. *Int J Mol Sci.* 2022 Apr 11;23(8):4226.
14. Lee T, Jammal AA, Medeiros FA. Association between serum vitamin D level and rates of structural and functional glaucomatous progression. *J Glaucoma.* 2022 Jul 1;31(7):614-621.