Hindawi
Journal of Ophthalmology
Volume 2020, Article ID 8071280, 8 pages
https://doi.org/10.1155/2020/8071280

Review Article

Vitamin D and Glaucoma: A Critical Review of the Literature

Hana Abouzeid [1,2] **and Caroline Flora Samer** [3,4]

[1]*Ophthalmology Division, Geneva University Hospitals-HUG, Geneva, Switzerland*
[2]*Clinical Eye Research Centre Memorial Adolphe de Rothschild, Geneva, Switzerland*
[3]*Clinical Pharmacology and Toxicology Division, Geneva University Hospitals-HUG, Geneva, Switzerland*
[4]*Faculty of Medicine, Geneva University, Geneva, Switzerland*

Correspondence should be addressed to Hana Abouzeid; hana.abouzeid@hcuge.ch

Received 31 January 2020; Revised 18 August 2020; Accepted 24 September 2020; Published 16 November 2020

Academic Editor: Steffen Heegaard

Primary open-angle glaucoma is a progressive optic neuropathy which can lead to irreversible blindness if untreated. A number of studies have been published suggesting a correlation between the level of serum vitamin D3 and glaucoma or intraocular pressure (IOP). The latter is known to be a major risk factor for glaucoma and is the main target of glaucoma treatment. We give a critical review of the literature, exploring what is known about this matter. While some studies report an inverse association between serum vitamin D3 and IOP, others do not confirm this finding. Similar divergent conclusions came from studies regarding the association between serum vitamin D3 and the presence or severity of glaucoma. The effect of vitamin D3 on IOP decrease has been attributed to both aqueous humor production and trabecular meshwork outflow pathway increase. Vitamin D3 has been shown to play a major role in reducing inflammation, modulating the immune response, and decreasing angiogenesis in the eye and in other organs. It has been suggested that, through its neuroprotective effect, vitamin D3 could be a protective factor for glaucoma and that vitamin D3 deficiency could explain glaucoma occurrence or severity in some patients. Other neurodegenerative diseases such as Alzheimer's disease and multiple sclerosis have been similarly related to vitamin D3 deficiency. 1α,25$(OH)_2$ vitamin D3 (calcitriol) supplementation has been shown to be beneficial for lowering IOP in monkeys. Although the studies highlighted in this review show interesting results, their limitations underscore the need for both population-based studies and larger randomized controlled trial with vitamin D3 supplementation. The specific role of vitamin D3 in the pathology of glaucoma remains to be elucidated, together with the possible therapeutic benefit of vitamin D3 supplementation.

1. Introduction

Glaucoma is an acquired and progressive optic neuropathy, which can lead to irreversible blindness. Its burden in the world population is growing as the population ages and no causative treatment has yet been identified [1]. Some of the main risk factors of glaucoma are advanced age, positive family history, higher cup-to-disk ratio, central corneal thickness, and elevated intraocular pressure (IOP), the latter being the only one which can be modified [2]. Lowering IOP has been proven to be effective in reducing glaucoma progression [3], hence the importance of identifying and understanding the IOP modifiers. Among numerous factors which have been reported to influence IOP, one can mention systemic blood pressure; time of day; supine position; caffeine, alcohol, nicotine, or cannabis consumption; steroid medication; age; genetic background; ethnicity; body mass index; diabetes [4]; and more recently vitamin D3 levels.

An inverse association between vitamin D3 levels in its hydroxylated form (25-hydroxyvitamin D3 or calcifediol, abbreviated 25(OH)D3) and IOP, and hence glaucoma, has recently been claimed in several studies [5–10]. Indeed, direct measurement of serum/plasma vitamin D levels is very difficult for clinical laboratories. 25(OH)D levels are measured because most vitamin D produced in the body is converted to 25(OH)D and its determination is feasible. Higher serum 25(OH)D levels have been described in fair-skinned Americans compared to Mexican Americans and to

non-Hispanic dark-skinned Americans, the latter having the lowest serum levels [11]. It is well known that fair-skinned people need less UVB exposure to produce the same amount of vitamin D3 compared with dark-skinned people, a fact which however remains poorly explained to date. Based on the prevalence of glaucoma [12] and the observation that the mean IOP is higher among African Americans compared to non-African populations [13], one might expect the vitamin D3-IOP interaction to shed light on this matter. Several studies have been published in the literature about vitamin D3 and IOP or glaucoma in humans [5–10], with different methodology and results.

In this context, we present a critical review of the literature in order to summarize our current knowledge on the interaction between IOP or glaucoma and vitamin D3.

1.1. Pharmacokinetics and Pharmacodynamics of Vitamin D. Vitamin D is a group of fat-soluble prohormones including vitamin D3 (cholecalciferol) and vitamin D2 (Figure 1). Vitamin D can either be produced in the skin from 7-dehydrocholesterol under the influence of UV light, so-called vitamin D3 (cholecalciferol), or directly absorbed from the diet as vitamin D3 and vitamin D2 (ergocalciferol) [14]. Either form is then hydroxylated to 25-hydroxycholecalciferol (calcidiol or calcifediol, 25(OH)D) in the liver by the cytochrome P450 (CYP) 2R1 mainly and 27A1. It is then transformed mainly in the kidney by 25-hydroxyvitamin D3-1α-hydroxylase (CYP27B1) to 1α,25-dihydroxyvitamin D ($1,25(OH)_2D$ or calcitriol), the active form of vitamin D3. CYP27B1 is expressed to a lesser degree in extrarenal tissues such as the epidermis, brain, pancreas, colon, breast, ovary, muscle, and immune cells/macrophages, as well as nonparenchymal hepatic cells [15]. Therefore a local production of $1,25(OH)_2D$ in these tissues is possible [16]. The excess of active vitamin D ($1,25(OH)_2D$) is converted into inactive metabolites ($1,24,25(OH)_3D$) by 24-hydroxylase (CYP24A1). The induction of CYP24A1 by $1,25(OH)_2D$ is a feed forward mechanism. The feedback mechanism is $1,25(OH)_2D$ inhibition of its own production by CYP27B1. CYP24A1 also converts 25(OH)D to another inactive metabolite, 24,25-dihydroxyvitamin D3, which is an additional mechanism to prevent excessive circulating levels of moderate or highly active vitamin D metabolites. Disproportionate administration of the hormonal form of vitamin D ($1,25(OH)_2D$) can cause vitamin D deficiency, that is through stimulating the degradation of 25(OH)D. This is important because most assays used to measure circulating 25(OH)D to estimate vitamin D status have a 100% cross reactivity with 24,25-dihydroxyvitamin D2.

Parathyroid hormone (PTH) stimulates CYP27B1 expression and decreases CYP24A1, to produce more active calcitriol [17].

$1,25(OH)_2D$ is the ligand for the vitamin D receptor (VDR), a transcription factor with hormone and DNA-binding domains. $1,25(OH)_2D$ binds to the vitamin D binding protein to reach its target cell, which then binds to cytoplasmic VDR to form a complex after entering the cell [18]. This complex then enters the nucleus where it heterodimerizes with the retinoid X receptor (RXR) and that heterodimer binds to DNA and thus regulates DNA transcription of hundreds of vitamin D dependent genes and largely influences gene expression in humans [19, 20]. $1,25(OH)_2D$ activates or represses transcription depending on the target gene. VDR is encoded by a gene located on chromosome 12 and over 63 polymorphisms have been reported. Most VDR polymorphisms only mildly modify the affinity of 1,25(OH)2D for the VDR, but some are associated with the inability for 1,25(OH)2D to bind VDR and may influence bone and mineral homeostasis. Only VDR mutations significantly compromise binding causing severe defects in bone and mineral homeostasis. The most studied VDR polymorphisms are rs10735810, rs1544410, rs731236, and rs7975232 [21].

The active form of vitamin D3 has many physiological roles such as the regulation of calcium homeostasis and bone mineralization, but it is now recognized to have antiproliferative and immunomodulatory properties [22–24]. It is reported to affect a wide range of human diseases, including notably cancer, cardiovascular, infectious, and autoimmune diseases [25].

Ergocalciferol, calcidiol and, calcitriol vary in their PK parameters in terms of onset of action and half-lives [26] (see Table 1).

2. Association of Vitamin D and Glaucoma

2.1. Clinical Studies. Table 2 summarizes the findings of the clinical studies discussed below.

In a study performed in Norway, Krefting at al. [8] divided healthy Caucasians with high or low serum 25(OH)D levels, recruited from a population-based study, into two groups. The IOP in the 87 participants with low serum 25(OH)D levels (mean 40.1 ± 12.9 nmol/l) did not differ from the IOP in the 42 participants with high serum 25(OH)D levels (mean 85.1 ± 14.0 nmol/l) (15.9 ± 3.3 mmHg versus 15.6 ± 3.1 mmHg, $p = 0.56$, independent t-test). The authors then performed a randomized clinical trial and measured the change in IOP after administration to the group with low serum 25(OH)D levels, twice a week over a period of 6 months, of either high dose vitamin D (one capsule of vitamin D3 20 000 IU-Dekristol; Mibe, Brehna, Germany) or placebo. At 6 months, the levels achieved upon the supplementation provided for 6 months to these individuals with low 25(OH)D at baseline 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). Although IOP slightly decreased after vitamin D administration, no statistical difference in IOP was reported with or without 25(OH)D administration ($p = 0.92$, independent t-test). However, the small size of each treatment arm ($n = 39$) and the selection bias inherent to the case-control methodology limit the conclusion one can draw from this study. Moreover, the most important data missing in the study is whether the vitamin D supplementation provided effectively corrected vitamin D deficiency and if there were significant differences in the decreases in IOP among those

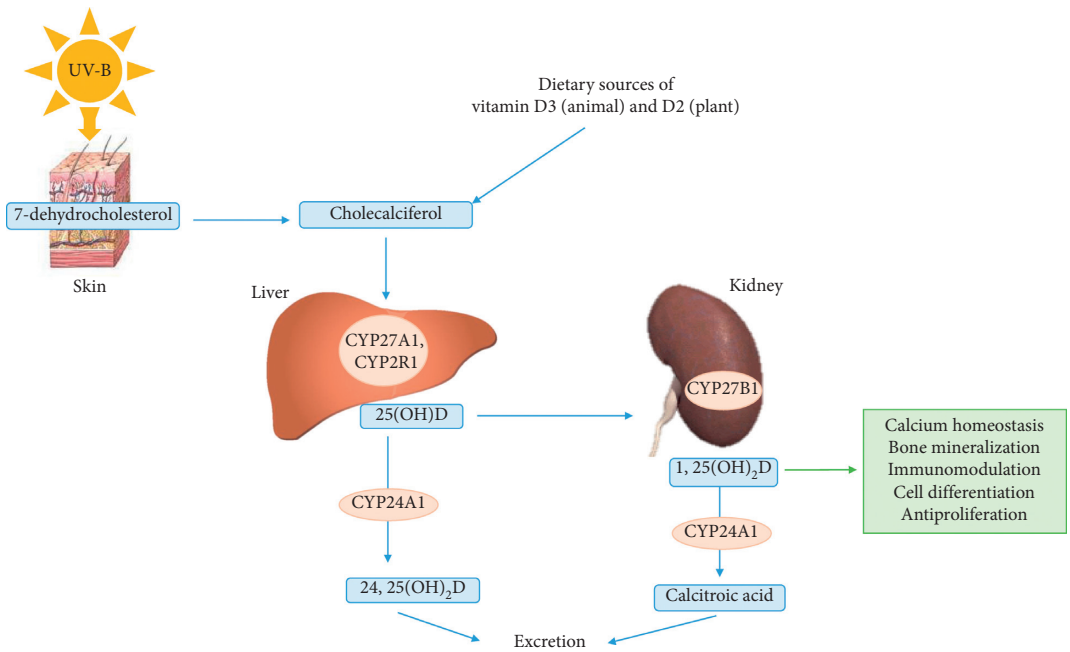

Figure 1: Normal vitamin D metabolism. Vitamin D can either be produced in the skin from 7-dehydrocholesterol under the influence of UV light, so-called vitamin D3 (cholecalciferol), or from ergosterol or directly absorbed from the diet as vitamin D3 and vitamin D2 (ergocalciferol). Either form is then hydroxylated to 25-hydroxycholecalciferol (calcidiol or calcifediol, 25(OH)D) in the liver by the cytochrome P450 (CYP) 27A1. It is then transformed mainly in the kidney by 25-hydroxyvitamin D3-1α-hydroxylase (CYP27B1) into 1α,25-dihydroxyvitamin D (1,25$(OH)_2$D or calcitriol).

Table 1: Vitamin D agents and half-lifes.

Agent	Half-life
Vitamin D2 (ergocalciferol) Vitamin D3 (cholecalciferol)	3–4 days
25(OH)D2 (ercalcidiol)	14 days
25(OH) D3 (calcifediol/calcidiol)	30 days
1,25$(OH)_2$D (calcitriol)	7–10 h

individuals who corrected the deficiency and those who remained insufficient or deficient.

Yoo et al. [10] reported in 2014 an inverse association between serum 25(OH)D concentration and primary open-angle glaucoma (POAG) ($n = 290$) in males only (OR = 0.98 with $p = 0.04$ for 1 ng/mL increase in 25(OH)D). The same inverse association with IOP was described in all three categories of participants which they considered. Their results were obtained in a cross-sectional study of 6,094 South Korean participants, including 290 open-angle glaucoma, 410 glaucoma suspect, and 5,394 healthy controls. However, and among other bias factors, the nonconsensual glaucoma definition used, the limited clinical expertise in glaucoma of the examiners (nonglaucoma specialists or residents), and the cross-sectional design of the study limit the conclusions which can be drawn from this study.

A larger retrospective cross-sectional study of 123,331 South Korean participants [7] found that lower 25(OH)D levels were significantly associated with an elevated risk of glaucoma in females only, found no association between IOP and vitamin D, and suggested that vitamin D may thus have a role in glaucoma pathogenesis independently of IOP levels. However, their study population had a large difference in the numbers of female and male subjects, and the group with high IOP was significantly smaller than the group with normal IOP. In addition, the subjects were diagnosed with glaucoma based only on fundus photographs, without any gonioscopic description of the angle. This limits the reliability of the assumed patient categorization and thus the conclusions on the association between vitamin D and the risk of glaucoma. Since angle closure is known to have an effect on IOP, it is difficult to hypothesize on the effect of vitamin D without a detailed gonioscopic description. In particular, angle-closure glaucoma should be excluded from vitamin D-glaucoma studies. In addition to the limitations in glaucoma definition mentioned, the cross-sectional design of the study and the fact that vitamin D supplementation was not taken into account preclude the determination of a direct association between vitamin D and open-angle glaucoma. There should be clear specification on exclusion or inclusion of vitamin D supplementation in published studies and data about whether the vitamin D supplementation provided effectively corrected vitamin D deficiency and if there were significant differences in the decreases of the studied outcome among those individuals who corrected the deficiency and those who remained insufficient or deficient. If there is a significant inverse association between glaucoma or IOP and low vitamin D levels, even if there were supplemented patients included in the study, this would strengthen the conclusions of an inverse association between vitamin D levels and glaucoma or IOP.

A French population case-control study [6] reported an association between the presence, but not the severity, of

Table 2: Summary of the reviewed clinical studies and their findings.

		Inverse association with 1. IOP 2. Glaucoma presence 3. Glaucoma severity	No. of patients	Type of study	Studied population	Tested serum vit D
1	[8]	1. N 2. NA 3. NA	129 healthy 87 low serum vit D 42 high serum vit D	Nested case-control and RCT	Norway	25(OH)
2	[10]	1. Y 2. Y 3. NA	POAG 290 Suspect 410 Healthy 5394	Cross-sectional	South Korea	25(OH)
3	[6]	1. N 2. Y 3. N	POAG 150 Severe 99 Moderate 51	Case-control	France	25(OH)
4	[7]	1. N 2. Y (in males only) 3. NA	Controls 164 Glaucoma 1627 Healthy 121,704	Cross-sectional	South Korea	25(OH)
5	[9]	1. NA 2. Y 3. NA VDR polymorphisms BsmI 'B' and TaqI 't'	POAG 79* Healthy 71	Case-control	China	1α,25(OH)2D3
6	[5]	1. Y 2. N 3. Y	POAG 357 Healthy 178	Case-control	African descent	25(OH)

*Unspecified gonioscopic status.

primary open-angle glaucoma and 25(OH)D serum levels. The 150 glaucoma patients had fifteen percent lower serum 25(OH)D concentration than the 164 controls (42.9 ± 25.7 nmol/L versus 49.4 ± 29.5 nmol/L, $p = 0.039$), as well as a greater prevalence of vitamin D insufficiency (90.7% of the glaucoma patients versus 82.3% of the controls, $p = 0.032$). Meanwhile, vitamin D insufficiency was found in 86.3% of all study participants. There was no difference regarding 25(OH)D serum levels or vitamin D insufficiency between the 99 patients with severe POAG and the 51 with moderate POAG. The serum concentration of 25(OH)D did not correlate with either intraocular pressure or visual field mean deviation, while POAG patient had treatment for controlling IOP, which significantly hinders the analysis of potential IOP lowering effect of 25(OH)D. The regular use of vitamin D supplementation by patients and controls was reported by direct inquiry, whatever the dosage, schedule, or route of administration and regardless of the date of commencement. Vitamin D supplementation was then added as a covariable in the statistical analysis. Despite the fact that the results were statistically adjusted for the presence of a vitamin D supplementation, the details of this supplementation are missing, limiting any conclusions about its efficacy and influence on the studied outcomes. The case-control design of this study and the small number of participants limit its robustness as well.

An American case-control study [5] reported an association between 25(OH)D serum level with the severity of glaucoma in a cohort of 357 POAG patients of African descent, but not with its presence. The mean (95% confidence interval [CI]) levels of vitamin D of the subjects in the control (8.02 ± 6.19 pg/ml) and early phenotype (7.56 ± 5.74 pg/ml) groups were significantly or marginally significantly different from the levels observed in subjects with the advanced phenotype (6.35 ± 4.76 pg/ml; $p = 0.0117$ and 0.0543, respectively). However, it should be noted that the serum levels of the 178 normal subjects were not significantly different from those of early glaucoma patients ($p = 0.8508$). In the latter study [5], the authors found a small yet significantly different from zero association between serum levels of 25(OH)D and IOP (correlation coefficient: −0.0819, p value: 0.0018). This study confirmed, in a population of African descent, the hypothesis of the role played by vitamin D in explaining the higher IOP observed among African Americans compared to non-African populations [13]. However, it relates this possible role to the severity of an existing glaucoma rather than to the occurrence of glaucoma. It should be noted that both studies [5, 6] used different definitions for glaucoma severity and included patients with different glaucoma severity. This may explain the difference found in their results. In the study of Ayyagari et al. [5], the authors compared 25(OH)D levels in early (better than −4 dB) and advanced primary open-angle glaucoma (worse than −10 dB) patients, while the French study [6] compared 25(OH)D levels in moderate (better than −12 dB) and advanced glaucoma (worse than −12 dB) patients. Other aspects which might explain the different results are on the one hand the fact that the populations studied were very different and on the other hand the glaucoma classifications used in these studies. At least in an

(unreported) number of cases, glaucoma classification was based on clinical appreciation only. These aspects weaken the reliability of the results.

Indeed, selection bias is inherent to case-control studies, especially when the study groups are relatively small, as in both cases discussed here, so the conclusions reached by the authors should be interpreted carefully. However, the suggestion by Ayyagari et al. [5] that, as a result of increased inflammation and neurodegeneration, the absence of the neuroprotective effect of vitamin D could explain glaucoma severity rather than occurrence is certainly interesting. In this context, it is worth mentioning the work of Uro et al. [27], which report serum 25(OH)D deficiency associated with a reduced ganglion cell complex (GCC) thickness in a cohort of 85 elderly French participants, as measured by high-definition optical coherence tomography ($72.1 \pm 7.4\,\mu$m versus $77.5 \pm 7.5\,\mu$m, $p = 0.028$). Participants were separated into 2 groups according to serum 25(OH)D levels. Only 11 participants were in the deficient group (deficient 25 nmol/l or sufficient > 25 nmol/l); open-angle glaucoma and age-related macular degeneration patients were excluded; the mean age was $71.13\,y \pm 4.71$. Of note is that vitamin D deficiency was not associated with reduced retinal fiber layer (RNLF) thickness. The authors speculated that they detected a neuronal loss affecting the GCC, possibly at an early stage preceding the thinning of the RNFL, which usually occurs in any optic neuropathy. The same group had previously published a study of reduced optical coherence tomography macular thickness in association with vitamin D deficiency [28]. These observations are in line with the speculative theory attributing a neurodegenerative effect of vitamin D insufficiency [5, 6, 27].

In a case-control study of 73 POAG, and 71 controls in the Han population of China, Lv et al. [9] reported $1\alpha,25(OH)_2D_3$ serum levels in POAG patients ($p < 0.001$) fifteen percent lower than in healthy controls (26.37 ng/ml ± 5.83 versus 30.43 ng/ml ± 3.91). Of note is that these levels are within the normal range. Interestingly, they also found a higher frequency of the vitamin D receptor BsmI 'B' (rs1544410) and TaqI 't' (rs731236) polymorphisms in the POAG group than in the control group. Participants who had undertaken vitamin D3 or analogs were excluded from this study. Based on their findings, the authors suggested that the presence of these alleles and the vitamin D deficiency represent risk factors of primary open-angle glaucoma. However, it should be noted that this suggestion was made despite the small number of participants in each group, and the fact that serum $1\alpha,25(OH)_2D_3$ levels were within the normal range, and vitamin D deficiency was not measured. Indeed, circulating $1\alpha,25(OH)_2D_3$ levels are normal in vitamin D deficient individuals unless there is a persistent severe vitamin D deficiency, and the measurements of 1,25D levels in circulation are of poor, if any, value, since its half-life is of a few hours. Authors do not report serum 25(OH)D levels which are relevant for vitamin D deficiency. In addition, the VDR polymorphisms presented in this study may indicate only nonfunctional associations as they do not affect VDR expression or actions.

Our knowledge of the effect of vitamin D deficiency on corneal thickness is limited. Cankaya et al. [29] have observed a lower corneal endothelial cell density and other endothelial indices in a case-control study of 58 patients with vitamin D level below 15 ng/ml compared to 40 normal controls. However, central corneal thickness was not statistically different between the two groups, indicating a preserved function of the endothelium. One can hypothesize that the endothelial function and thus the central corneal thickness could be altered according to the level of vitamin D deficiency. Of note is that the intraocular level of vitamin D metabolites is unknown and certainly influences the consequence on the endothelium. This study has major limitations, the main one being its small size, and its results need to be reproduced and confirmed by other larger studies. If central corneal thickness is increased as a result of vitamin D deficiency, this could constitute a major bias that may have misled the authors, as they have attributed higher IOP to vitamin D instead of simply increased corneal thickness. Nevertheless, Kocaturk et al. [30] reported no statistically significant difference in corneal compensated IOP measured by ocular response analyzer between three groups with, respectively, 41 subjects with serum vitamin $D < 20$ ng/ml, 39 subjects with serum vitamin $D > 20$ and < 30 ng/ml, and 40 healthy controls with serum vitamin $D > 30$ ng/ml. The method of measurement and the measured vitamin D were not specified.

2.2. Experimental Studies. An experimental study on seven monkeys has shown significant reduction of IOP after $1\alpha,25(OH)_2D$ or its analog 2-methylene-19-nor-(20S)-1α,25-dihydroxyvitamin D3 (2MD) was topically applied [31] in one eye compared to placebo in the other eye, with lacrimal duct occlusion. The effect of $1,25(OH)_2D$ (5 mg) lasted more than 12 hours and was more effective than 2MD in lowering IOP (20% versus 15%). No control group other than the contralateral eyes was used in this study. The reduction in IOP was not attributed to reduced aqueous humor formation as measured by fluorometry nor to increased uveoscleral outflow, which was reduced by topical use of pilocarpine, suggesting an effect of the administered products on aqueous humor drainage. The authors also found, based on *in vivo* and *in vitro* microarray analysis, that $1,25(OH)_2D$ regulates genes that are known to be involved in the determination of IOP. $1,25(OH)_2D$ markedly suppressed the expression of the angiotensin I converting enzyme (ACE), the carbonic anhydrase (CAI), and the Ras homolog gene family, member A (RHOA) and significantly increased the expression of the chemokine (C-C motif) ligand 20 (CCL20). $1\alpha,25(OH)_2D$ strongly downregulated the expression of the cytoskeleton genes (alpha and gamma actins), the cell adhesion genes (CEACAM and CD44), and the major extracellular matrix (ECM) genes (RHOA and fibronectin I. $1,25(OH)_2D$ also increased the expression of several other ECM genes, viz., the matrix metalloproteinases 3, 11, 13, and 14, while decreasing the expression of their inhibitor TIMP3. It was found that ECM remodeling in the trabecular meshwork can decrease outflow resistance and

thus increase aqueous humor outflow. Other genes affected by 1,25(OH) $_2$D that could be involved in regulating IOP are the purinergic receptors P2Y, the G-protein coupled, 2 (P2RY2), and the aquaporin 1 channel (AQP1). Of note is a clinical case-control study of Caucasian participants with 382 POAG and 363 healthy controls in which there was no association between common polymorphisms in the AQP1 gene and POAG [32]. This suggests that if vitamin D plays a causative role in POAG, its effect probably does not involve a single gene down- or upregulation, but rather follows a more complex pathway. Undoubtedly, 1,25(OH)$_2$D modulates the expression of genes with multiple benefits on the eye. Nevertheless, these correlations do not demonstrate that correction of vitamin D deficiency should help delay the onset of the defects that 1,25(OH) $_2$D controls, because serum 1,25D levels remain normal despite vitamin D deficiency, except in cases of prolonged severe vitamin D deficiency with 25(OH)D levels below 4 ng/ml. Indeed, it is impossible to measure the amount of local 1,25D production within the eye required to mimic the benefits of topical 1,25D. Consequently, it would be very difficult also to know what would be the levels of circulating 25(OH)D levels that ensure the required local 1,25D production within the eye.

In an experimental study on human tissue, Lv et al. [33] reported a protective effect of 1,25(OH)$_2$D on human trabecular meshwork cells which underwent damage from an oxidative stress induced by inhibition of the TGFbeta-SMAD3-VDR pathway. The latter is the primary pathway regulating extracellular matrix deposition in human trabecular meshwork. Again, reshaping the extracellular matrix of the trabecular meshwork can decrease outflow resistance and thus increase aqueous humor outflow through the conventional pathway.

These two experimental studies seem to strongly relate the effect of vitamin D on IOP to both the conventional outflow pathway, and thus to the trabecular meshwork, and the aqueous humor formation, based on the vitamin D modulation of multiple genes expression. Aqueous humor drains mainly through the trabecular meshwork; any deposition within it, increasing outflow resistance, could cause higher IOP, which in turn is a major risk factor for glaucoma development and progression.

3. Discussion

Out of the five clinical studies described above which treated the subject, only two showed an inverse association between serum level of 25(OH)D and IOP [5, 10], and only one showed an association between 25(OH)D and both IOP and glaucoma [10]. The experimental study on monkeys dealt with topical application of 1,25(OH)$_2$D; it found a 20% reduction of IOP after treatment, which seems to confirm the relation between vitamin D and IOP [31]. The study of human trabecular meshwork suggested a higher aqueous humor outflow through trabecular meshwork [33].

A total of four clinical studies out of five showed a direct association between serum levels of 25(OH)D and the presence of glaucoma [6, 7, 9, 10] (see Table 2). Only two studies reported on vitamin D and both glaucoma presence and severity [5, 6]. Only one of these two reported an association between vitamin D and glaucoma severity [5]. The latter studies suggest that vitamin D has an independent effect on the occurrence of glaucoma, unrelated to the IOP. No study could assess vitamin D level as an independent risk factor for glaucoma incidence or progression. All studies harbored significant differences in the sample size, study design, vitamin D measurements (enzyme-linked immunosorbent assay vs. radioimmunoassay), measured forms of vitamin D (25(OH)D versus 1,25(OH)$_2$D), and study population, which influenced the outcome. Conclusions one draws should thus be very careful.

However, published studies suggest vitamin D could have an effect on IOP through gene expression of aqueous humor production or outflow modulation, or through its neuroprotective effect. Vitamin D has been linked to inflammation modulation through different factors [34–37]. Inflammation factors are known to influence neurodegeneration and its severity, and vitamin D has been suggested to be an influencing factor for inflammation and degeneration of neuronal tissue [38, 39]. In addition, vitamin D deficiency was reported in various studies to be associated with major neurodegenerative diseases, such as Alzheimer's disease [40, 41], multiple sclerosis [42], and clinically isolated syndrome [43]. Supplementation of vitamin D on Alzheimer's and multiple sclerosis is reported to be beneficial [40, 42], although larger studies are needed to confirm this conclusion. Through its role in inflammatory, immune, and antioxidant properties, vitamin D is thus expected to play a key role in neuroprotection. Indeed, vitamin D is believed to exert a protective role against several ocular diseases or conditions by modulating the immune system and inhibiting inflammation and angiogenesis [44]. Similar to its effect on other neurodegenerative diseases, vitamin D deficiency could thus be a significant factor in glaucoma pathogenesis, including its development, progression, and severity. The fact that GCC thinning has been reported in vitamin D deficient patients [27] supports this hypothesis. It is noteworthy that, in Alzheimer's disease, retinal ganglion cell loss and RNFL thinning have been described with OCT [45, 46]. A cumulative contribution of multiple factors is not excluded, as is the possibility of different effect in different ethnicities according to the genetic background. This could explain the different findings on the effect of vitamin D levels on either IOP or glaucoma occurrence.

Only one published study, a case-control study [9], deals with serum 1,25(OH)$_2$D levels as measured in humans. In fact, little is known about the presence of the converting enzyme from 25(OH)D to 1,25(OH)D in the human eye. In rabbit, mouse, and human corneal cell lines, Yin et al. [47] showed that both 25(OH)D_3 and 1,25(OH)$_2$D were present in the eye, as well as vitamin D receptor and 1-alpha-hydroxylase, the enzyme required to convert 25(OH)D to 1,25(OH)$_2$ D. Based on a human corneal cell line, Lin et al. [48] showed that human corneal epithelial cells were capable of synthesizing vitamin D3 metabolites (25(OH)D_3 and 24,25(OH)D_3) following UV-B exposure, in the presence of 7-dehydrocholesterol.

Indeed, the intraocular conversion of circulating 25(OH)D to $1,25(OH)_2D$ could have important local benefits with minimal risk of hypercalcemia if there is sufficient production to mimic the effects of topical $1,25(OH)_2D$ application. The systemic conversion of supplemented vitamin D to 25(OH)D provides the eye with the amount of substrate required for its local conversion to 1,25D for VDR transactivation of the vitamin D responsive genes that are critical for normal eye function. If correction of systemic vitamin D deficiency is not adequate, the local levels of 25(OH)D may not be sufficient for the eye to generate the local 1,25D needed. This would explain the observed lack of effect of 25(OH)D systemic administration on IOP [8] and inversely the effect observed on monkey by applying topical $1,25(OH)_2D$ [31]. Meanwhile, in rabbits fed with a vitamin D-supplemented diet, 25(OH)-vitamin D3 and $1,25(OH)_2$-vitamin D3 increased in aqueous humor [48].

This question calls for future prospective observational studies including 25(OH)D dosage in both normal populations and glaucoma patients. Since $1,25(OH)_2D$ has already been described as attenuating stress-induced damage in human trabecular meshwork cells [33], experimental therapy in glaucoma animal models with systematic, topical, and/or intraocular supplementation of $1,25(OH)_2D$ would be of interest in order to characterize the effect of $1,25(OH)_2D$ on IOP and eventual glaucoma progression. It could also pave the way to potential new therapeutic vitamin D related pathways. Larger prospective population-based studies of different ethnicities are needed in order to confirm and further determine the strength of the presumed association in normal and glaucoma patients.

In summary, despite contradicting clinical reports, it seems that vitamin D metabolites may play a role in glaucoma, through either a lowering effect of IOP or a neuroprotection pathway. However, all the clinical studies discussed in this review had a rather limited number of participants and significant bias determined by the chosen study design, precluding the conclusions regarding the involvement of vitamin D in primary angle glaucoma or in IOP. Experimental studies confirm an association between vitamin D and IOP and open the way to pathophysiological explanations of its occurrence. However, the exact molecular mechanism underlying this potential association is still unknown. In this context, population-based studies are needed to give us information on IOP and glaucoma and their eventual association with vitamin D metabolites. Targeting vitamin D could represent a new therapeutic pathway for glaucoma which, given the burden of glaucoma disease, deserves to be thoroughly investigated.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

The authors are grateful to the Mémorial de Recherche Clinique en Ophtalmologie, Mémorial Adolphe de Rothschild, Geneva, Switzerland.

References

[1] Y.-C. Tham, X. Li, T. Y. Wong, H. A. Quigley, T. Aung, and C.-Y. Cheng, "Global prevalence of glaucoma and projections of glaucoma burden through 2040," *Ophthalmology*, vol. 121, no. 11, pp. 2081–2090, 2014.

[2] A. L. Coleman and S. Miglior, "Risk factors for glaucoma onset and progression," *Surv Ophthalmol*, vol. 53, no. Suppl 1, pp. S3–10, 2008.

[3] M. C. Leske, A. Heijl, M. Hussein et al., "Factors for glaucoma progression and the effect of treatment," *Archives of Ophthalmology*, vol. 121, no. 1, pp. 48–56, 2003.

[4] R. Hoehn, A. Mirshahi, E. M. Hoffmann et al., "Distribution of intraocular pressure and its association with ocular features and cardiovascular risk factors," *Ophthalmology*, vol. 120, no. 5, pp. 961–968, 2013.

[5] R. Ayyagari, Y. I. Chen, L. M. Zangwill et al., "Association of severity of primary open-angle glaucoma with serum vitamin D levels in patients of African descent," *Molecular Vision*, vol. 25, pp. 438–445, 2019.

[6] A. Goncalves, D. Milea, P. Gohier et al., "Serum vitamin D status is associated with the presence but not the severity of primary open angle glaucoma," *Maturitas*, vol. 81, no. 4, pp. 470–474, 2015.

[7] H. T. Kim, J. M. Kim, J. H. Kim et al., "The relationship between vitamin D and glaucoma: a kangbuk samsung health study," *Korean Journal of Ophthalmology*, vol. 30, no. 6, pp. 426–433, 2016.

[8] E. A. Krefting, R. Jorde, T. Christoffersen, and G. Grimnes, "Vitamin D and intraocular pressure—results from a case -control and an intervention study," *Acta Ophthalmologica*, vol. 92, no. 4, pp. 345–349, 2014.

[9] Y. Lv, Q. Yao, W. Ma, H. Liu, J. Ji, and X. Li, "Associations of vitamin D deficiency and vitamin D receptor (Cdx-2, Fok I, Bsm I and Taq I) polymorphisms with the risk of primary open-angle glaucoma," *BMC Ophthalmology*, vol. 16, p. 116, 2016.

[10] T. K. Yoo, E. Oh, and S. Hong, "Is vitamin D status associated with open-angle glaucoma? A cross-sectional study from South Korea," *Public Health Nutrition*, vol. 17, no. 4, pp. 833–843, 2014.

[11] R. Scragg, M. Sowers, and C. Bell, "Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the third national health and nutrition examination survey," *Diabetes Care*, vol. 27, no. 12, pp. 2813–2818, 2004.

[12] M. C. Leske, A. M. Connell, A. P. Schachat, and L. Hyman, "The Barbados eye study," *Archives of Ophthalmology*, vol. 112, no. 6, pp. 821–829, 1994.

[13] M. C. Leske, A. M. S. Connell, S.-Y. Wu, L. Hyman, and A. P. Schachat, "Distribution of intraocular pressure," *Archives of Ophthalmology*, vol. 115, no. 8, pp. 1051–1057, 1997.

[14] K. Makris, C. Sempos, and E. Cavalier, "The measurement of vitamin D metabolites: part I-metabolism of vitamin D and the measurement of 25-hydroxyvitamin D," *Hormones (Athens)*, vol. 19, no. 2, pp. 81–96, 2020.

[15] G. Jones, "Extrarenal vitamin D activation and interactions between vitamin D2, vitamin D3, and vitamin D analogs," *Annual Review of Nutrition*, vol. 33, no. 1, pp. 23–44, 2013.

[16] A. Dusso, A. Brown, and E. Slatopolsky, "Extrarenal production of calcitriol," *Seminars in Nephrology*, vol. 14, no. 2, pp. 144–155, 1994.

[17] S. Christakos, P. Dhawan, A. Verstuyf, L. Verlinden, and G. Carmeliet, "Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects," *Physiological Reviews*, vol. 96, no. 1, pp. 365–408, 2016.

[18] S. Sirajudeen, I. Shah, and A. Al Menhali, "A narrative role of vitamin D and its receptor: with current evidence on the gastric tissues," *International Journal of Molecular Sciences*, vol. 20, no. 15, p. 3822, 2019.

[19] M. A. Maestro, F. Molnár, A. Mouriño, and C. Carlberg, "Vitamin D receptor 2016: novel ligands and structural insights," *Expert Opinion on Therapeutic Patents*, vol. 26, no. 11, pp. 1291–1306, 2016.

[20] J. W. CraigLanders and M. B. Meyer, "Fundamentals of vitamin D hormone-regulated gene expression," *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 144, pp. 5–11, 2014.

[21] M. Abouzid, M. Karazniewicz-Lada, and F. Glowka, "Genetic determinants of vitamin D-related disorders; focus on vitamin D receptor," *Current Drug Metabolism*, vol. 19, no. 12, pp. 1042–1052, 2018.

[22] S. Christakos, M. Hewison, D. G. Gardner et al., "Vitamin D: beyond bone," *Annals of the New York Academy of Sciences*, vol. 1287, no. 1, pp. 45–58, 2013.

[23] S.-M. Jeon and E.-A. Shin, "Exploring vitamin D metabolism and function in cancer," *Experimental & Molecular Medicine*, vol. 50, no. 4, p. 20, 2018.

[24] M. Miraglia Del Giudice, C. Indolfi, and C. Strisciuglio, "Vitamin D: immunomodulatory aspects," *Journal of Clinical Gastroenterology*, vol. 52, no. Suppl 1, pp. S86–S88, 2018, Proceedings from the 9th Probiotics, Prebiotics and New Foods, Nutraceuticals and Botanicals for Nutrition & Human and Microbiota Health Meeting, held in Rome, Italy from September 10 to 12, 2017.

[25] D. D. Bikle, "Vitamin D metabolism, mechanism of action, and clinical applications," *Chemistry & Biology*, vol. 21, no. 3, pp. 319–329, 2014.

[26] S. Mazzaferro, D. Goldsmith, T. E. Larsson, Z. A. Massy, and M. Cozzolino, "Vitamin D metabolites and/or analogs: which D for which patient?" *Current Vascular Pharmacology*, vol. 12, no. 2, pp. 339–349, 2014.

[27] M. Uro, O. Beauchet, M. Cherif, A. Graffe, D. Milea, and C. Annweiler, "Age-related vitamin D deficiency is associated with reduced macular ganglion cell complex: a cross-sectional high-definition optical coherence tomography study," *PLoS One*, vol. 10, no. 6, Article ID e0130879, 2015.

[28] A. Graffe, O. Beauchet, B. Fantino, D. Milea, and C. Annweiler, "Vitamin D and macular thickness in the elderly: an optical coherence tomography study," *Investigative Opthalmology & Visual Science*, vol. 55, no. 8, pp. 5298–5303, 2014.

[29] C. Cankaya, T. Cumurcu, and A. Gunduz, "Corneal endothelial changes in patients with vitamin D deficiency," *Indian Journal of Ophthalmology*, vol. 66, no. 9, pp. 1256–1261, 2018.

[30] T. Kocaturk, S. Bekmez, and M. Unubol, "Effects of vitamin D deficiency on intraocular pressure values obtained by ocular response analyzer," *International Ophthalmology*, vol. 40, no. 3, pp. 697–701, 2019.

[31] G. D. Kutuzova, B. A. T. Gabelt, J. A. Kiland, E. A. Hennes-Beann, P. L. Kaufman, and H. F. DeLuca, "1α,25-Dihydroxyvitamin D3 and its analog, 2-methylene-19-nor-(20S)-1α,25-dihydroxyvitamin D3 (2MD), suppress intraocular pressure in non-human primates," *Archives of Biochemistry and Biophysics*, vol. 518, no. 1, pp. 53–60, 2012.

[32] W. Liu, Y. Liu, X. J. Qin, S. Schmidt, M. A. Hauser, and R. R. Allingham, "AQP1 and SLC4A10 as candidate genes for primary open-angle glaucoma," *Molecular Vision*, vol. 20, no. 16, pp. 93–97, 2010.

[33] Y. Lv, X. Han, Q. Yao et al., "1α,25-dihydroxyvitamin D3 attenuates oxidative stress-induced damage in human trabecular meshwork cells by inhibiting TGFβ-SMAD3-VDR pathway," *Biochemical and Biophysical Research Communications*, vol. 516, no. 1, pp. 75–81, 2019.

[34] F. Colotta, B. Jansson, and F. Bonelli, "Modulation of inflammatory and immune responses by vitamin D," *Journal of Autoimmunity*, vol. 85, pp. 78–97, 2017.

[35] W. Liu, L. Zhang, H. J. Xu et al., "The anti-inflammatory effects of vitamin D in tumorigenesis," *International Journal of Molecular Sciences*, vol. 19, no. 9, p. 2736, 2018.

[36] M. Mangin, R. Sinha, and K. Fincher, "Inflammation and vitamin D: the infection connection," *Inflammation Research*, vol. 63, no. 10, pp. 803–819, 2014.

[37] T. K. Wöbke, B. L. Sorg, and D. Steinhilber, "Vitamin D in inflammatory diseases," *Frontiers in Physiology*, vol. 5, p. 244, 2014.

[38] T. L. Briones and H. Darwish, "Vitamin D mitigates age-related cognitive decline through the modulation of pro-inflammatory state and decrease in amyloid burden," *Journal of Neuroinflammation*, vol. 9, p. 244, 2012.

[39] K.-P. Jiao, S.-M. Li, W.-Y. Lv, M.-L. Jv, and H.-Y. He, "Vitamin D3 repressed astrocyte activation following lipopolysaccharide stimulation in vitro and in neonatal rats," *Neuroreport*, vol. 28, no. 9, pp. 492–497, 2017.

[40] M. O. W. Grimm, A. Thiel, A. A. Lauer et al., "Vitamin D and its analogues decrease amyloid-beta (abeta) formation and increase abeta-degradation," *International Journal of Molecular Sciences*, vol. 18, no. 12, p. 2764, 2017.

[41] T. J. Littlejohns, W. E. Henley, I. A. Lang et al., "Vitamin D and the risk of dementia and Alzheimer disease," *Neurology*, vol. 83, no. 10, pp. 920–928, 2014.

[42] B. S. Martina, M. Rametta, and A. T. Anthony, "Reder vitamin D and multiple sclerosis: a comprehensive review," *Neurology and Therapy*, vol. 7, no. 1, pp. 59–85, 2018.

[43] K. O'Connell, J. Sulaimani, S. A. Basdeo et al., "Effects of vitamin D(3) in clinically isolated syndrome and healthy control participants: a double-blind randomised controlled trial," *Multiple Sclerosis Journal—Experimental, Translational and Clinical*, vol. 3, no. 3, 2017.

[44] M. Nebbioso, G. Buomprisco, A. Pascarella, and N. Pescosolido, "Modulatory effects of 1,25-dihydroxyvitamin D3 on eye disorders: a critical review," *Critical Reviews in Food Science and Nutrition*, vol. 57, no. 3, pp. 559–565, 2017.

[45] V. T. T. Chan, Z. Sun, S. Tang et al., "Spectral-domain OCT measurements in alzheimer's disease," *Ophthalmology*, vol. 126, no. 4, pp. 497–510, 2019.

[46] A. Kesler, V. Vakhapova, A. D. Korczyn, E. Naftaliev, and M. Neudorfer, "Retinal thickness in patients with mild cognitive impairment and Alzheimer's disease," *Clinical Neurology and Neurosurgery*, vol. 113, no. 7, pp. 523–526, 2011.

[47] Z. Yin, V. Pintea, Y. Lin, B. D. Hammock, and M. A. Watsky, "Vitamin D enhances corneal epithelial barrier function," *Investigative Opthalmology & Visual Science*, vol. 52, no. 10, pp. 7359–7364, 2011.

[48] Y. Lin, J. L. Ubels, M. P. Schotanus et al., "Enhancement of vitamin D metabolites in the eye following vitamin D3 supplementation and UV-B irradiation," *Current Eye Research*, vol. 37, no. 10, pp. 871–878, 2012.