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Review

Vitamin D: Implications for ocular disease and therapeutic potential

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ABSTRACT

Vitamin D is a multifunctional hormone that is now known to play a significant role in a variety of biological functions in addition to its traditional role in regulating calcium homeostasis. There are a large number of studies demonstrating that adequate vitamin D levels are important in maintaining health and show that vitamin D is able to be utilized at local tissue sites. In the eye, we have increasing evidence of the association between disease and vitamin D. In this narrative review, we summarize recent findings on vitamin D and its relationship to various ocular pathologies and the therapeutic potential for some of these, as well as examine the basic science studies that demonstrate that vitamin D is biologically relevant in the eye.

1. Introduction

While first identified for its role in calcium homeostasis, vitamin D is now recognized to have many diverse functions including effects on immune regulation, proliferation, differentiation, apoptosis, and angiogenesis (Plum and DeLuca, 2010; Prietl et al., 2013). Vitamin D directly or indirectly regulates up to 5% of the human genome, or over 900 different genes (Wang et al., 2005). In addition, the vitamin D receptor (VDR) is almost ubiquitously expressed (Bouillon et al., 2008). The enzyme necessary for conversion of vitamin D to its functional metabolite has been identified in a number of cell types, which are able to utilize circulating vitamin D to form the biologically active hormone. Extrarenal activation, expression, and gene influence suggest that vitamin D function is widespread, with pleiotropic effects within the tissue microenvironment where it is activated.

Vitamin D is obtained from two sources: dietary consumption (fatty fish, fortified foods, supplementation, for example) and local production in the skin (Fig. 1) (Kamen and Tangpricha, 2010; White, 2008). Exposure to ultraviolet B radiation (UVB 290–315 nm) generates vitamin D from 7-dehydrocholesterol through a series of thermal and photochemical reactions in the epidermis. Subsequently, vitamin D undergoes two hydroxylation steps to form the active hormone (Kamen and Tangpricha, 2010; Schauber and Gallo, 2008). In the liver, vitamin D is hydroxylated to 25-hydroxyvitamin D_3 ($25D_3$), the primary circulating form, by cytochrome p450 enzymes CYP2R1 and CYP27A1 (Bouillon et al., 2008). Further modification to form the fully functional 1,25-dihydroxyvitamin D_3 ($1,25D_3$) classically occurs in the kidneys, mediated by 1-alpha-hydroxylase, CYP27B1; however, there are an increasing number of extrarenal tissues that are being identified that are also able to activate vitamin D. 24-hydroxylation, catalyzed by CYP24A1, regulates vitamin D metabolite levels through catabolism of both $25D_3$ and $1,25D_3$, leading to the excretion of the 24-hydroxylated products (Jones et al., 2014; Prosser and Jones, 2004). Active vitamin D binds to its nuclear hormone receptor, VDR, which heterodimerizes with retinoic X receptor, and binds to both positive and negative vitamin D response elements (VDRE) in target genes. VDR then recruits co-activators, mediator complex, and chromatin-modifying enzymes to influence gene transcription (Kim et al., 2005).

Vitamin D status is assessed by measuring circulating $25D_3$ concentrations, which has a much longer half-life than $1,25D_3$ (~2 weeks versus ~4 h) and is present in higher circulating concentrations (Holick et al., 2011). Although the range of values varies slightly, in general, optimal serum $25D_3$ levels should be between

Abbreviations: VDR, vitamin D receptor; UVB, ultraviolet B radiation; $25D_3$, 25-hydroxyvitamin D_3; $1,25D_3$, 1,25-dihydroxyvitamin D_3; VDRE, vitamin D response element; SNP, single-nucleotide polymorphism; AMD, age-related macular degeneration; HTRA1, high-temperature requirement factor A1; DR, diabetic retinopathy; AAU, acute anterior uveitis; DHCR7, 7-dehydrocholesterol reductase; EAU, experimental autoimmune uveitis; IOP, intraocular pressure.

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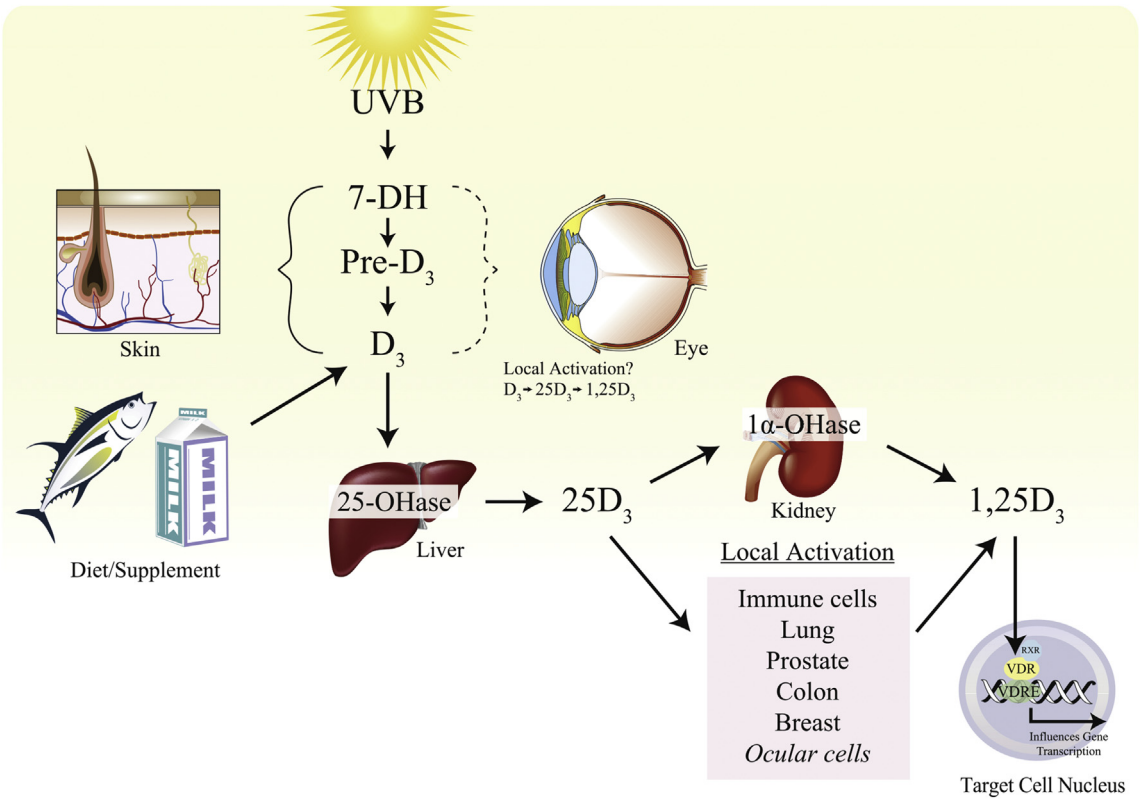

Fig. 1. Vitamin D_3 production and activation. UVB from sunlight penetrates the skin, converting a cholesterol precursor, 7-dehydrocholesterol (7-DH), to pre-vitamin D_3 (pre-D_3), which then isomerizes to form vitamin D_3 (D_3). Recent evidence suggests that ocular surface cells also produce vitamin D_3 *de novo* when exposed to UVB. Vitamin D_3 must undergo two enzymatic steps to form the biologically active hormone. The skin, and possibly the cornea, is able to activate and utilize vitamin D_3 locally. However, the majority of vitamin D_3 is transported to the liver, where the 25-hydroxylases (25-OHase) CYP2R1 and CYP27A1, catalyze the formation of 25-hydroxyvitamin D_3 ($25D_3$), the major circulating form. Activation of $25D_3$ traditionally occurs in the kidney through the 1α-hydroxylase, CYP27B1 (1α-OHase), although many extra-renal tissues and cell types are also able to activate $25D_3$, including cells of the eye. The functionally active 1α-dihydroxyvitamin D_3 ($1,25D_3$) then binds to its nuclear hormone receptor, VDR, in target cells, influencing gene transcription through interactions with vitamin D response elements (VDRE).

30 and 80 ng/mL (75–200 nmol/L), with deficiency/insufficiency recognized to be $25D_3$ < 20 ng/mL (50 nmol/L) (Gröber et al., 2013; Holick, 2007; Kennel et al., 2010). The Institute of Medicine, Food and Nutrition Board recommends the adequate intake of vitamin D for most people to be 600IU per day to maintain a healthy status, with an increased intake of 800IU per day for individuals over age 70 (Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, 2011).

There is a growing body of research on locally produced vitamin D and its tissue specific effects (Adams and Hewison, 2012). In the eye, vitamin D target cells were first identified by the presence of vitamin D-dependent calcium binding protein, or calbindin, which was shown to be expressed throughout the human retina (Verstappen et al., 1986). Immunohistochemical staining later identified the presence of VDR in the epithelium of the cornea, lens, ciliary body, and retinal pigment epithelium, as well as the corneal endothelium, ganglion cell layer, and retinal photoreceptors in the human eye (Johnson et al., 1995). Recently, the presence of vitamin D hydroxylases (CYP27B1, CYP27A1, CYP2R1, and CYP24A1) has been demonstrated in corneal epithelial, endothelial, scleral fibroblasts, nonpigmented ciliary body epithelial, and adult retinal pigment epithelial cell lines (Alsalem et al., 2014; Yin et al., 2011), suggesting that ocular cells have the machinery to activate and regulate vitamin D metabolism. Indeed, most of these cell types were found to be able to convert $25D_3$ into the functionally active $1,25D_3$ (Alsalem et al., 2014). Excitingly, corneal limbal epithelial cells were able to produce vitamin D, *de novo*, in culture when exposed to UVB, similar to cells of the skin (Lin et al., 2012), potentially providing a local source of vitamin D to the ocular surface (Fig. 1). Other sources of vitamin D in the eye could be the aqueous and vitreous humor and tear film, in which vitamin D metabolites have been shown to be present in rabbits and increase with oral vitamin D supplementation (Lin et al., 2012; Yin et al., 2011).

With the expression of the receptor and vitamin D regulatory enzymes throughout the eye, studying vitamin D in relation to ocular tissues and pathologies is biologically significant. There is increasing evidence that vitamin D is important in the maintenance of ocular health. This review summarizes epidemiological and basic science studies on vitamin D (Table 1) with a focus on the pathophysiology of various eye diseases and conditions and potential therapeutic roles for this versatile molecule.

2. Vitamin D studies in the eye

2.1. Myopia

Myopia development is multifactorial, with a combination of genetic and environmental factors playing a role in increased axial elongation. Epidemiological studies have shown that time spent outdoors is protective against myopia development (French et al., 2013; Guggenheim et al., 2012; Rose et al., 2008; Sherwin et al., 2012). Therefore, vitamin D status and pathway genetic variations are being examined in relation to myopia to determine if vitamin D plays a role. In a small multiple regression study, subjects with myopia (<−0.75 diopter) had lower serum $25D_3$ levels compared to

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Table 1
Summary of studies examining various aspects of vitamin D as it relates to ocular disease, health, and the basic biology of the eye.

Vitamin D status	Low serum $25D_3$ levels associated with disease risk; or high $25D_3$ levels associated with decreased disease prevalence	Myopia[a] Age-related macular degeneration[b] Diabetic retinopathy[c] Dry eye syndrome[d]
Genetic variations[e]	Gene polymorphisms associated with disease (VDR, CYP24A1, CYP27B1, DHCR7)	Myopia[a] Age-related macular degeneration[b] Diabetic retinopathy[c] Uveitis[f]
Treatment/Supplementation	Improvement of disease or pathology with either systemic or local vitamin D treatment	Retinoblastoma (mouse)[g] Choroidal melanoma (mouse)[g] Retinal aging (mouse)[b] Ischemic retinopathy (mouse)[b] Type 2 diabetic retinopathy (rat)[c] Experimental autoimmune uveitis (mouse)[f] Corneal injury (mouse)[d] Corneal transplantation (rat)[d] Corneal neuralgia (human case report)[d] Intraocular pressure (non-human primate)[h]
In vitro cell studies	Expression of vitamin D pathway components and/or biological effect of vitamin D treatment	Corneal epithelial cells[d,i] Lens epithelial cells[i] Corneal endothelial cells[i] Scleral fibroblasts[i] Nonpigmented ciliary body epithelial cells[i] Adult retinal pigment epithelial cells[b,i] Ganglion cell layer[i] Retinal photoreceptors[i] Retinoblastoma cells (Y79, Weri-RB1)[g]

[a] See 2.1 Myopia.
[b] See 2.3 Age-related macular degeneration.
[c] See 2.4 Diabetic retinopathy.
[d] See 2.6 Ocular surface inflammation and pathology.
[e] Table 2.
[f] See 2.5 Uveitis.
[g] See 2.2 Retinoblastoma.
[h] See 2.7 Glaucoma.
[i] See 1 Introduction.

non-myopes after adjustment for dietary intakes. While these results suggested vitamin D status could be related to myopia risk, a larger study was needed to confirm this (Mutti and Marks, 2011).

In 2014, a study was published correlating vitamin D levels and myopia in 2038 Korean subjects (Choi et al., 2014). Vitamin D deficiency is very common in the Korean population, particularly adolescents, and myopia rates are increasing (Choi et al., 2011; Yoon et al., 2011). Testing the hypothesis that vitamin D plays a role in myopia risk, Choi et al. (2014) found that spherical equivalent was positively correlated with serum $25D_3$ levels in myopic participants from the Korea National Health and Nutrition Examination Survey (2008–2011), after adjusting for age and sex. This association was particularly significant in the high myopia group. In addition, serum $25D_3$ concentration was also significantly associated with myopia after adjusting for confounding factors such as socioeconomic level, rural versus urban residence, daily milk and calcium intakes, and smoking history. Several variables were not taken into account (time spent outdoors and sunlight exposure) which have been shown to affect myopia development and vitamin D levels and therefore could have influenced the results of this study. However, although the association is small, this study, as Mutti commented, was important in providing evidence that vitamin D could be a potential therapeutic option to control the increasing rates of myopia (Mutti, 2014).

Another large study examined the association between vitamin D levels and myopia in participants from the Western Australian Pregnancy Cohort (Raine) Study (Yazar et al., 2014). In this study, the authors analyzed potentially confounding variables, such as age, parental myopia, ethnicity, education, time spent outdoors, and ocular sun exposure, measured by conjunctival UV autofluorescence (CUVAF) score. Seasonal variability in serum $25D_3$ concentrations was also taken into account in the analysis. With a total of 946 total participants, myopic participants had significantly lower serum $25D_3$ levels than nonmyopic subjects. In addition, the likelihood of being myopic decreased with increasing $25D_3$ levels in multivariable regression models adjusting for time spent outdoors and CUVAF as well as the fully adjusted model. It is important to note that serum $25D_3$ concentrations increased with increasing CUVAF; therefore, as Yazar comments, further studies examining vitamin D levels and sun exposure preceding myopia development would be very helpful in determining vitamin D's importance in protecting against myopia.

Guggenheim et al. performed a large study using prospective data from the Avon Longitudinal Study of Parents and Children (ALSPAC) to determine if the protective effect of time spent outdoors on myopia was mediated by vitamin D (Guggenheim et al., 2014). They found, as others have reported, that time spent outdoors was associated with increased $25D_3$ levels and reduced incidence of myopia. Also, vitamin D levels were negatively correlated with myopia. However, the protective effect of time spent outdoors was not attenuated when serum $25D_3$ or $25D_2$ was added to the model. This study suggests that vitamin D is not the protective factor in time spent outdoors in regards to myopia development. Several important limitations of this study, such as determination of time spent outdoors using a single questionnaire and refractive error without cycloplegia, should be mentioned here. Further studies that address the causality of protection from time outdoors are definitely warranted.

Genetic polymorphisms in vitamin D pathway genes have been associated with an increased risk for various ocular pathologies, as well as vitamin D status (Table 2). Several studies have examined variations in the VDR as potential risk factors for myopia

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Table 2
Genetic polymorphisms in vitamin D pathway genes and their known associations with ocular diseases.

Pathology	Gene; variation	Association	Publication
Myopia	VDR; *FOK1*	None with high myopia Increased frequency of f allele in myopic females	Annamaneni et al., 2011
	VDR; rs2853559 rs2239182 rs3819545 rs2853559	Associated with Caucasian subjects > -0.75 D myopia in both eyes Associated with Caucasian subjects between −0.75 D and −4.00 D	Mutti et al., 2011
AMD	CYP24A1; rs6127118 rs2762934	Associated with neo-vascular AMD in family-based cohort	Morrison et al., 2011
	rs1570669 rs1570670 rs2274130 rs2296239 rs4809957	Significantly associated with AMD in meta-analysis	
	VDR; rs2189480	Associated with neo-vascular AMD in family-based cohort; not significant in all AMD subtypes	
Diabetic retinopathy	VDR; *FOK1*	Decreased incidence of advanced DR in type 1 diabetics	Taverna et al., 2005
	VDR; Bsml	Associated with DR in type 1 diabetics	Bucan et al., 2009
	VDR; Taq I	Frequency of TT, wildtype genotype, was lower in type 1 patients with severe DR	Taverna et al., 2002
Uveitis	CYP27B1; rs703842 A > G	Increased frequency in HLA-B27-positive AAU patients compared to controls	Steinwender et al., 2013
	DHCR7; rs12785878	Associated with ocular Behçet's disease patients	Fang et al., 2014

development. The VDR gene is located near loci identified to be associated with myopia (MYP-3) (Annamaneni et al., 2011). In addition, deregulated calcium homeostasis has been implicated in ciliary muscle dysfunction, leading to problems with emmetropization and mechanical stress (Dulhunty et al., 2006). Therefore, in addition to the protective effect of time spent outdoors, vitamin D's ability to regulate calcium levels also suggests that it could be involved in myopia progression. In a multivariate analysis of a Caucasian cohort, a single-nucleotide polymorphism (SNP) in the VDR was found to be significantly associated with the presence of myopia. In a subgroup of myopes from this study (between −0.75 and −4.00 D), three SNPs in the VDR were identified that were significantly linked to myopia (Mutti et al., 2011). The *Fok1* VDR polymorphism, however, which has been found to affect calcium homeostasis (Gross et al., 1996; Jurutka et al., 2001), was not found to confer risk for either high or low myopia, although the frequency of the f allele was higher in females, particularly in those subjects with low myopia (Annamaneni et al., 2011).

An interesting topic for expanded exploration is the relationship of vitamin D status to the global and ethnic differences seen in myopia rates. Although vitamin D deficiency is a widespread health issue, low serum levels are more frequent in Asian and Middle Eastern populations (Mithal et al., 2009). Darker skin coloration, higher latitudes, low sun exposure, age, and diet all contribute significantly to deficiency (Kift et al., 2013; Lee et al., 2014; Mithal et al., 2009). Similarly, myopia development is associated with a range of both environmental and genetic components (Sherwin and Mackey, 2013) and rates are increasing worldwide, particularly in East and Southeast Asian populations (Choi et al., 2011; Yoon et al., 2011). In total, data suggest a link between vitamin D status and myopia; however the biological significance and mechanism of this protection needs to be addressed and further studies are needed to confirm these findings.

2.2. Retinoblastoma

First identified for its ability to regulate calcium absorption, vitamin D is now recognized to have antineoplastic activity against many types of cancers. It has been shown to influence cell differentiation, induce apoptosis, inhibit angiogenesis, and arrest cell growth in various tumors (Frampton et al., 1983; Krishnan et al., 2010; Leyssens et al., 2013; Nagakura et al., 1986; Picotto et al., 2012; Szyszka et al., 2012). In 1966, Verhoeff hypothesized that vitamin D could be an effective treatment for retinoblastoma based on the observation that tumors undergoing spontaneous regression frequently had calcifications (Verhoeff, 1966). Although it has since been shown that vitamin D treatment does not induce tumor calcification (Albert et al., 1992), vitamin D has been proven effective both *in vitro* and in animal models of retinoblastoma in inhibiting tumor cell growth (Sabet et al., 1999).

Early studies showed the presence of VDR in Y79 cells, a human retinoblastoma cell line, both in culture and in tumors of Y79 cells injected subcutaneously into athymic nude mice, a xenograft model of the disease (Albert et al., 2002; Saulenas et al., 1988; Wagner et al., 2003). Y79 and Weri-RB1 cells also expressed the CYP24A1 gene (Morrison et al., 2011). Human retinoblastoma tissue and tumors from LH beta-Tag transgenic mice, a model in which the overexpression of the SV40 T antigen induces retinal tumors similar to human disease (Suárez et al., 2007; Windle et al., 1990), also expressed the receptor, suggesting that these tumors would be responsive to vitamin D treatment (Albert et al., 2002; Wagner et al., 2003). $1,25D_3$ treatment did inhibit Y79 cell growth *in vitro*, inducing G0/G1 cell cycle arrest, and apoptosis, or programmed cell death, of the tumor cells. Mechanistically, $1,25D_3$ upregulated Bax, a pro-apoptotic protein, while decreasing the expression of anti-apoptotic Bcl-2, contributing to the increase in cell death (Albert et al., 2002). In both the xenograft and transgenic models of disease, systemic administration of $1,25D_3$ for 5 weeks significantly inhibited tumor growth. $1,25D_3$ treatment increased apoptosis of cancer cells (Audo et al., 2003) and inhibited angiogenesis within tumors (Shokravi et al., 1995). Unfortunately, however, even low doses of $1,25D_3$ (0.05 μg/day) were toxic and resulted in an increase in mortality and hypercalcemia, as measured by serum calcium and renal calcifications (Albert et al., 2002, 1992; Cohen et al., 1988; Sabet et al., 1999).

An active area of vitamin D research has been the development

of VDR agonists which have similar protective actions of $1,25D_3$ but have lower calcemic effects. In mouse models of retinoblastoma, several vitamin D analogs have shown promise in reducing tumor growth while having less toxic systemic effects compared to $1,25D_3$ (Sabet et al., 1999). Specifically, 1,25-dihydroxy-16-ene-23-yne-vitamin D_3 (16,23-D_3) (Albert et al., 2004, 2002; Sabet et al., 1999; Shternfeld et al., 1996; Wilkerson et al., 1998), 1α-hydroxyvitamin D_2 (1α−OH−D_2) (Albert et al., 2004, 2002; Dawson et al., 2003), and 2-methylene-19-nor-(20S)-1α-hydroxybishomopregnacalciferol (2MbisP) (Albert et al., 2005) reduced retinoblastoma tumor size without toxicity. 1α−OH−D_2 has also been shown to inhibit pigmented intraocular tumor growth in a transgenic model mimicking human choroidal melanoma (Albert et al., 2004). Combination therapies are also a possibility in the treatment of retinoblastoma, where a very low concentration of vitamin D could enhance tumor responsiveness to chemotherapy. One such study has shown that $1,25D_3$ administered with Cisplatin significantly reduced tumor growth, while no mortality or toxicity to the kidneys was observed (Kulkarni et al., 2009).

2.3. Age-related macular degeneration

Because of its protective role during inflammation, oxidative stress, fibrosis, and angiogenesis, vitamin D has been studied in relation to age-related macular degeneration (AMD). While not classically considered an inflammatory disease, it is now recognized that inflammatory events, such as complement activation, immune cell recruitment, and proinflammatory cytokine release, play a role in the development of AMD (Coleman et al., 2008; Nussenblatt et al., 2009; Wang et al., 2011). Therefore, Parekh et al. first hypothesized that vitamin D could be protective against AMD progression (Parekh et al., 2007). In an analysis using 7752 individuals from the third National Health and Nutrition Examination Survey (1988−1994), those subjects in the highest quintile of serum $25D_3$ levels had decreased prevalence of early AMD and drusen versus those in the lowest quintile. However, this inverse relationship between vitamin D levels and early AMD was not observed with advanced AMD, possibly accounted for by the much smaller number of subjects with advanced AMD. Examining the association between consumption of foods high in vitamin D and AMD prevalence, this study also found an inverse relationship between milk consumption and early AMD using a food frequency questionnaire, which asked subjects to recall dietary intakes in the month prior to the study (Parekh et al., 2007).

Based on these results, other epidemiological studies have been performed examining the connection between vitamin D levels and AMD. Day et al. (2012) examined the rate of first diagnosis of both neovascular and nonneovascular AMD in Medicare patients based on vitamin D status. Although they did not find a significant association between AMD incidence and vitamin D deficiency, this retrospective study was not able to use patients' laboratory data, and therefore exact $25D_3$ concentrations were not used. In a case study evaluating monozygotic twins with varying AMD phenotypes, twins with less severe AMD and smaller drusen area had higher dietary vitamin D consumption (Seddon et al., 2011). Although, as noted by Annweiler, dietary vitamin D intake does not necessarily correspond to vitamin D status (Annweiler et al., 2012). In a separate retrospective study analyzing 1045 individuals with an AMD diagnosis, no association was found between serum $25D_3$ levels and disease (Golan et al., 2011). Although this was a large study, several limitations must be pointed out in interpreting the results. AMD was not categorized by severity and clinical data was not available for the analysis; therefore, early and late AMD cases were not separated. In addition, subjects′ use of vitamin D supplementation was not known.

In an evaluation of participants in the Carotenoids in Age-Related Eye Disease Study, when separated by age, higher serum $25D_3$ concentration was associated with decreased risk of early AMD in women younger than 75 years old (Millen et al., 2011). This association, however, was decreased when dietary patterns, BMI, and physical activity were accounted for. Also, most participants were Caucasian, postmenopausal women, and therefore, results were specific to a specialized population. A smaller retrospective study in France found that individuals with low vitamin D serum levels (<50 nmol/L) were also more likely to have AMD, but late-stage AMD in particular (Graffe et al., 2012). A large, cross-sectional study of participants in the Korean National Health and Nutrition Examination Survey (2008−2012), also found an inverse association between $25D_3$ levels and late AMD, however only in men and not with early AMD after adjustment for age, sun exposure, smoking, and heart disease (Kim et al., 2014).

Following up an earlier study, Graffe et al. used optical coherence tomography to measure pathological changes preceding disease and found that vitamin D insufficiency (<50 nmol/L) was associated with reduced macular thickness (Graffe et al., 2014). Singh et al. (2013) specifically examined subretinal fibrosis in patients with advanced AMD, classified into the Clinical Age-Related Maculopathy Staging (CARMS) group 5. In their single-center study, they found that patients with subretinal fibrosis had significantly lower serum vitamin D levels and were more likely to be vitamin D-insufficient (<50 nmol/L) than patients without fibrosis. This significance was maintained after adjusting for confounding factors such as age, smoking, diet, sex, exercise, and four SNPs known to influence systemic vitamin D concentrations. Interestingly, there was no difference in serum $25D_3$ concentrations between genotypes or between clinical groups 1–5. The authors suggest that this specifically links vitamin D deficiency with subretinal fibrosis. Vitamin D is known to play a role in inhibiting fibrosis in other tissues and low concentrations have been implicated in the pathogenesis of fibrotic diseases, partly through inhibition of transforming growth factor beta (TGF-β) (Artaza and Norris, 2009; Halder et al., 2011; Isik et al., 2012; Petta et al., 2010; Ramirez et al., 2010). Based on these results by Singh et al., studies aimed at determining how vitamin D levels influence tissue changes and fibrosis in AMD would be very interesting. They also warrant an examination of a possible protective role for vitamin D during fibrotic events in other eye diseases as well.

Morrison et al. further explored the relationship between vitamin D and AMD risk (Morrison et al., 2011). They found that in a cohort of 481 sibling pairs, neovascular AMD risk went down with increasing ultraviolet irradiance, as measured by UV index. Although not statistically significant, serum vitamin D levels tended to be higher in unaffected subjects. In a larger scale study, which included three different cohorts for a total of 2528 subjects and was controlled for known AMD risk factors (smoking, gender, and age), single point variations, SNPs, in the CYP24A1 gene, but not VDR, correlated with an increased risk for all AMD subtypes in a meta-analysis. Polymorphisms in 24A1 were located chromosomally in a region that was known previously to have AMD susceptibility loci (Iyengar et al., 2004; Seddon et al., 2003). This study importantly showed a genetic link between AMD prevalence and vitamin D metabolism.

Several genetic variations have been identified as strong risk factors for AMD. In one of these loci, a single-nucleotide polymorphism in the promoter of the *HTRA1* gene (High-temperature requirement factor A1) has been found to significantly increase the likelihood of AMD development (Chen et al., 2009; Dewan et al., 2006; Tong et al., 2010; Yang et al., 2006). The orthologous *HTRA1* promoter region in the rhesus monkey contains 9 VDR binding sites and interestingly, one of these sites is removed by the AMD-

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associated *HTRA1* SNP (Pahl et al., 2013). *In vitro* studies demonstrated that stimulation with vitamin D lowered the activity of the wild type *HTRA1* in ARPE-19 cells. Further studies are needed to identify if vitamin D signaling influences this promoter region and if disease associated variations affect these pathways. Additionally, more studies are needed to firmly establish that vitamin D status is a risk factor for AMD development and to determine if vitamin D supplementation affects the development of AMD.

Several interesting studies have examined inflammatory events and neovascularization in the mouse retina with vitamin D treatment. In a study using aging mice, Lee et al. demonstrated that subcutaneous treatment with vitamin D significantly reduced signs of retinal inflammation (Lee et al., 2012). Treated mice had fewer macrophages in the subretinal space, less complement (C3d) deposition on Bruch's membrane, and a reduction in retinal amyloid beta accumulation. In addition, vitamin D treatment improved visual function, as measured by the electroretinogram a-wave. In a mouse model of oxygen-induced ischemic retinopathy, intraperitoneal vitamin D treatment inhibited retinal neovascularization in a dose-dependent manner (Albert et al., 2007). These mouse models suggest that vitamin D supplementation could be protective against both inflammation and angiogenesis in the retina, providing mechanisms of reduced vitamin D being involved in AMD development.

2.4. Diabetic retinopathy

Vitamin D's ability to inhibit neovascularization also has led researchers to examine the hormone's involvement in diabetic retinopathy (DR) development. In an epidemiological study, Aksoy et al. (2000) found that serum vitamin D concentrations ($25D_3$) were inversely related to the severity of retinopathy in diabetic patients, with the lowest concentrations of the hormone measured in patients with proliferative DR (Aksoy et al., 2000). Patients without associated retinopathy had the highest serum vitamin D concentrations. A similar study classified patients into diabetic groups based on disease severity and also found that patients with proliferative DR had the lowest mean $25D_3$ levels (21.1 ng/mL) (Payne et al., 2012). In addition, vitamin D deficiency was associated with increased risk of retinopathy in an adolescent population with type 1 diabetes (Kaur et al., 2011), however it was not associated with changes in retinal geometric parameters such as vascular branching angle, length-diameter ratio, or tortuosity (Poon et al., 2013).

Genetic variations in VDR have also been associated with diabetic retinopathy. In a cohort of Caucasian patients with type 1 diabetes, patients with the *Fok*I VDR polymorphism (FF genotype), had a lower incidence of advanced diabetic retinopathy, particularly in those patients whose duration of diabetes was less than 25 years (Taverna et al., 2005). The *Fok*I substitution is a functional polymorphism which has been reported to increase immune cell activity (van Etten et al., 2007) and therefore could have a protective effect on DR development. In other studies, the VDR *Bsml* gene polymorphism was also associated with risk of DR (Bućan et al., 2009) and the Taq I polymorphism with severe DR (Taverna et al., 2002).

Looking to an animal model to study vitamin D's ability to protect against retinopathy, Ren et al. used a rat model of type 2 diabetes (Ren et al., 2012). They found that animals treated with vitamin D had decreased retinal expression of VEGF and TGF-β1. Histological examination also suggested that vitamin D had a protective effect in the retinas of these rats. These combined studies suggest that vitamin D status could be important in the prevention of DR, particularly proliferative retinopathy. Further studies are needed to determine the mechanism of vitamin D protection and if it can directly inhibit neovascularization in this sight-threatening condition.

2.5. Uveitis

Uveitis is an inflammatory condition that affects the retina and uvea. Inflammation can be caused by an infectious agent or, in the majority of cases, is thought to be autoimmune in nature, driven by retinal antigen-specific T lymphocytes (Caspi, 2010). Because of its ability to dampen inflammation, influence T cell response, and its known ability to have suppressive actions in autoimmune conditions, vitamin D is a good candidate to examine in the context of this sight-threatening disease.

The most common form of uveitis, acute anterior uveitis (AAU), has been strongly associated with the human leukocyte antigen (HLA)-B27 gene (Chang et al., 2005; Suhler et al., 2003; Wakefield et al., 2011). In an interesting retrospective study, the association of a vitamin D hydroxylase gene polymorphism (CYP27B1 rs703842A > G) with HLA-B27-positive AAU was examined (Steinwender et al., 2013). This study found that individuals with AAU were more likely to have this CYP27B1 variation than HLA-B27-positive controls. Other studies have demonstrated that the rs703842A > G polymorphism results in lower levels of circulating $25D_3$ (Orton et al., 2008). Therefore, Steinwender et al. (2013) suggested that these HLA-B27 positive individuals could have an even greater impairment in immune function when vitamin D metabolism is disrupted.

Behçet's disease is an inflammatory disease that involves multiple organs in the body but over half of patients develop uveitis (Yazici et al., 2007). In a prospective study on a Chinese population, polymorphisms in an enzyme necessary for vitamin D production, DHCR7 (7-dehydrocholesterol reductase), were associated with susceptibility to ocular Behçet's disease in particular, demonstrating another genetic variation linking vitamin D metabolism and uveitis (Fang et al., 2014).

Experimental autoimmune uveitis (EAU) is a mouse model of human autoimmune uveitis in which the immune response has been well characterized. In this model, oral vitamin D treatment both prevented the development of disease as well as attenuated retinal autoimmunity once induced (Tang et al., 2009). Importantly, vitamin D inhibited the Th17 response that is responsible for the retinal inflammation in this model, influencing T cell cytokine production and the priming ability of dendritic cells. In similar studies using human samples from patients with Behçet's disease, vitamin D treatment also inhibited Th17 cell differentiation (Tian et al., 2012). These studies provide evidence that vitamin D supplementation could be beneficial not only during the active inflammatory condition but also for prevention of uveitis as well.

2.6. Ocular surface inflammation and pathology

Vitamin D is known to affect cell differentiation. In the cornea, VDR knockout mice had smaller superficial squamous cell size, decreased total corneal thickness, and lower numbers of tight junctions than wild-type animals (Lu and Watsky, 2014; Elizondo et al., 2014). Additionally, VDR influenced cell diffusion coefficients within the cornea, possibly playing a role in gap junction communications and development in this ocular tissue (Lu and Watsky, 2014). Interestingly, the rate of epithelial wound healing was decreased in VDR knockout animals (Elizondo et al., 2014). Mucin packaging in conjunctival goblet cells was also altered in VDR-deficient mice, with lower amounts of mucin (Muc5AC) in these animals compared to wild-types (Paz et al., 2003). However, both mucin and wound closure differences seemed to be attributable to vitamin D's influence on calcium homeostasis, as restoring

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ionized calcium levels in the VDR knockout mice restored normal mucin packaging as well as healing rates in these studies.

Inflammation at the ocular surface must be carefully regulated during infection and injury to prevent loss of corneal opacity and tissue damage. Based on vitamin D's known ability to suppress inflammation and influence the immune response, several groups have studied the immunomodulatory role of vitamin D within the local context of the ocular surface. *In vivo* studies have demonstrated that vitamin D can be anti-inflammatory at the ocular surface. In a mouse model of injury, topical administration of $1,25D_3$ to sutured mouse corneas inhibited Langerhans cell migration and maturation, and delayed neovascularization in the central cornea (Suzuki et al., 2000a). In a rat keratoplasty model, $1,25D_3$ protected against corneal graft rejection, inhibiting the proinflammatory cytokines interleukin-1 alpha (IL-1α) and tumor necrosis factor alpha (TNFα) (Dang et al., 2004).

In vitro, vitamin D appears to dampen the inflammatory response to infection. Treatment with vitamin D downregulated the expression of IL-1β, IL-6 and IL-8 induced by *Pseudomonas aeruginosa* infection in human corneal epithelial cells (Xue et al., 2002). In a separate report, $1,25D_3$ also inhibited IL-1α production (Suzuki et al., 2000b) and we have shown that vitamin D reduces Toll-like receptor induced inflammatory cytokines in cultured epithelial cells (Reins RY, McDermott AM. Vitamin D attenuates Toll-like receptor 3 induced inflammation in human corneal epithelial cells. Invest Ophthalmol Vis Sci 2013; e-abstract 2067). In addition, both $1,25D_3$ and $25D_3$ augmented corneal epithelial barrier function through upregulation of the tight junction proteins occludin and ZO-1 (Yin et al., 2011). Vitamin D therefore has the potential to reverse the harmful effects to the corneal epithelial barrier during infection and protect against inflammatory conditions.

In a cross-sectional study examining male patients with dry eye syndrome, a condition that is accompanied by ocular surface inflammation (DEWS report, 2007), serum $25D_3$ levels were not found to be associated with severity of disease clinically (Galor et al., 2014). However, higher serum vitamin D levels were significantly correlated with a decrease in subjective dry eye symptoms, as determined by the Dry Eye Questionnaire 5. In a case report, it was observed that a vitamin D-deficient patient with corneal neuralgia had relief from burning pain with vitamin D supplementation, 1000 IU/day, while topical therapies and lubricants were not effective (Singman et al., 2013). Although this is only a single observation without extensive follow-up, vitamin D's protective effect on ocular surface pain would be interesting to pursue further.

2.7. Glaucoma

Gene expression studies identified vitamin D as having the potential to modulate genes involved in regulating both aqueous humor outflow and production, as well as the architecture of the trabecular meshwork, thereby influencing IOP. In both cultured mouse calvarial cells and rat intestinal mucosa, treatment with vitamin D modulated the expression of numerous genes involved in intraocular pressure (IOP) regulation (Kutuzova et al., 2012). Microarray analysis showed that $1,25D_3$ decreased the expression of carbonic anhydrase I (CAI), angiotensin I converting enzyme (ACE), aquaporin 1 channel (AQP1), and various cytoskeletal and extracellular matrix genes such as actin alpha (ACTA1) and fibronectin I. $1,25D_3$ also upregulated matrix metalloproteinases 3, 11, 13, and 14, as well as prostaglandin E receptor 4 for PGE2 (PTGER4), purinergic receptors P2Y and P2RY2, and chemokine (C–C motif) ligand 20 (CCL20).

As a result of these gene expression studies, Kutuzova et al. (2012) examined the effect of $1,25D_3$ or an analog, 2-methylene-19-nor-(20S)-1α,25-dihydroxyvitamin D(3) on IOP in non-human primates. They demonstrated that topical $1,25D_3$, administered twice daily (0.1–15 μg $1,25D_3$ or vehicle propylene glycol) reduced IOP in monkeys. Significantly, when $1,25D_3$ was applied to one eye without nasolacrimal duct occlusion, IOP was lowered bilaterally. However, $1,25D_3$ did not reduce aqueous humor production or effect uveoscleral outflow in this model. Therefore, the mechanism involved in this decrease in IOP still needs to be investigated with further studies.

A very early study suggested that vitamin D, introduced intramuscularly, could decrease IOP in humans (Guist and Steffen, 1953). However, in a case control and randomized controlled study, Krefting et al. examined the association between serum vitamin D levels, vitamin D supplementation, and IOP and they found no statistical difference in IOP levels between individuals in the lowest serum $25D_3$ group versus the high serum $25D_3$ group (Krefting et al., 2013). Additionally, there was no significant change in IOP in participants who received vitamin D oral supplements (20,000 IU twice per week) at the end of 6 months compared to placebo.

Examining the association between vitamin D status and risk for open-angle glaucoma (OAG), Yoo et al. performed multivariable logistic regression analyses using 6094 participants from the Fifth Korean National Health and Nutrition Examination Survey (Yoo et al., 2014). They found a significant relationship between serum $25D_3$ levels and prevalence of OAG, with increased risk of disease particularly in participants in the lowest quintile of $25D_3$. Additionally, unlike the findings of Krefting et al. (2013), IOP was significantly linked to vitamin D levels. This apparent discrepancy could in part be due to differences in participant ethnicity (Caucasian versus South Korean), sample size, or the exclusion of participants with diagnosed disease in the Krefting study. Further epidemiological studies need to be done to determine if vitamin D status is a risk factor for glaucoma.

3. Conclusions

Vitamin D is a multifunctional hormone, which not only affects calcium homeostasis, but plays a role in immune system regulation as well as cell growth and survival. Many tissues in the eye are able to both activate and respond to vitamin D, suggesting that vitamin D is a biologically relevant molecule to study throughout the eye. Epidemiological studies demonstrate that vitamin D levels and genetic variations influence the development of a wide range of pathologies, such as myopia, age-related macular degeneration, diabetic retinopathy, and uveitis. In addition, at the cellular level, vitamin D is able to reduce inflammatory mediators, enhance barrier function, and induce cell death of cancerous cells. These studies suggest that vitamin D plays a protective role in ocular health. It will therefore be exciting to follow further work, examining the benefits of vitamin D therapeutically in the eye.

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