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Review

Can vitamin D protect against age-related macular degeneration or slow its progression?

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Dietary vitamin D plays an important role in maintaining proper vision. Age-related macular degeneration (AMD) is a complex eye disease with unknown pathogenesis. Studies on dietary supplementation and AMD occurrence and progression have produced conflicting results. In its advanced stage, AMD may be associated with apoptosis, pyroptosis or necroptosis of retinal cells. Vitamin D has been reported to play a role in modulating each of these programmed death pathways. Vitamin D is a modulator of the immune system and it acts synergistically with two members of the regulators of complement activation family H and I, whose specific variants are the most important genetic factors for AMD pathogenesis. Angiogenesis is an essential component of the neovascular form of AMD, the most devastating type of the disease and vitamin D is reputed to possess antiangiogenic properties. Cellular DNA damage response is weakened in AMD patients and so it is another process that can be modulated by vitamin D. Finally, impaired autophagy is claimed to play a role in AMD and emerging evidence suggests that vitamin D can influence autophagy. Therefore, several pathways of vitamin D metabolism and AMD pathogenesis overlap, suggesting that vitamin D could modulate the course of AMD.

Key words: dietary vitamin D, age-related macular degeneration, autophagy, inflammation, immune response

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Abbreviations: 1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; 8oxoG, 8-oxo-2′-deoxyguanosine; AMD, age-related macular degeneration; ATG, autophagy-related protein; CFH/I – complement factor H/I; CYP2R1, cytochrome P450 family 2 subfamily R member 1; DDR, DNA damage response; HTRA1, high temperature requirement protein A1; IL-1α, interleukin-1α; LC3, microtubule-associated protein light chain 3; mTOR, mechanistic target of rapamycin; NLRP3, NLR (neural retina leucine zipper) family pyrin domain containing 3; RPE, retinal pigment epithelium; SNP, single nucleotide polymorphism; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VDR, vitamin D receptor

INTRODUCTION

Age-related macular degeneration

Age-related macular degeneration (AMD) is a complex eye disease destroying the macula, the part of the retina responsible for sharp central vision and it is the leading cause of vision loss in the elderly in many countries (Reibaldi *et al.*, 2016). Although pathogenesis of AMD is largely unknown, an inappropriate diet can influence its occurrence and progression (Aoki *et al.*, 2016; Broadhead *et al.*, 2015; Everitt *et al.*, 2006; Parekh *et al.*, 2007; Seddon *et al.*, 2011; Stevens *et al.*, 2015). More detail on the role of diet in AMD pathogenesis is provided in a subsequent section.

AMD is an emerging medical problem as the number of people affected by AMD and the cost of medical care increase (Wong *et al.*, 2004). In its advanced stage, the disease occurs in two basic forms: dry (non-neovascular) and wet (neovascular). Whereas there have been some successes in the treatment of wet AMD with inhibitors of vascular endothelial growth factor A (VEGFA), important for neovascularization, there is no remedy for the dry form of the disease (Maguire & Campbell, 2010).

Genetic, environmental and life-style factors have been implicated in AMD pathogenesis (Fig. 1). AMD mainly affects individuals over 65 years old. Mutations in the genes coding for complement factors H and I as well as some other genes, including those participating in lipid metabolism, other components of the immune system, and parts of the vascular system, represent the main genetic risk factors for AMD (Lyzogubov *et al.*, 2016). Studies conducted in the United States indicate that white race and female sex seem to be strongly associated with the occurrence of AMD – in 2010, 2.5% of the white adults aged 50 or older had AMD, while the disease occurrence in blacks, Hispanics and people of other races was less than 1%; furthermore, the majority i.e. 65% of AMD cases occurred in women (https://nei.nih.gov/eyedata/amd). Changes in the cellular epigenetic pattern (epimutations) can also be important in the pathogenesis of AMD (Blasiak *et al.*, 2013b). Oxidative stress, protein aggregation and inflammation along with genetic risk factors, are all claimed to be involved in AMD pathogenesis (Kauppinen *et al.*, 2016). Drusen, small yellowish objects containing damaged material, are a characteristic feature of the disease and their presence is a clinical hallmark of AMD.

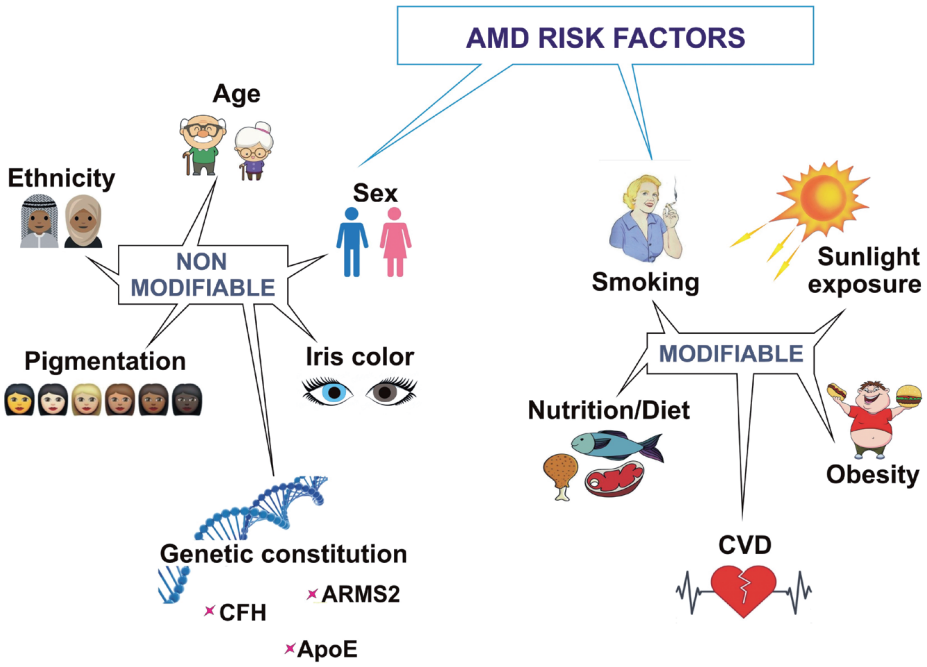

Figure 1. Age-related macular degeneration (AMD) risk factors.
AMD is a multifactorial disease with several genetic and environmental factors important for its pathogenesis. Advanced age, Caucasian ethnicity, female sex, light skin pigmentation, blue iris, fat-rich diet, smoking, UV and blue light exposure, as well as obesity and cardiovascular complications are some commonly accepted AMD risk factors. Mutations in the CFH (complement factor H), ARMS2 (age-related maculopathy susceptibility 2), ApoE (apolipoprotein E) genes are associated with AMD occurrence. CVD – cardiovascular diseases.

Progression of AMD leads to a massive macular degeneration accompanied by dysfunctional retinal pigment epithelium (RPE) cells and photoreceptors, which may die in the end stage of the disease. The death of the retinal cells in AMD is likely executed by apoptotic, pyroptotic or necroptotic program, but it is not known whether any one of these mechanisms predominates in the AMD pathology (Kaarniranta *et al.*, 2017).

Vitamin D

Vitamin D is claimed to possess a protective potential in many human diseases, including various cancers, cardiovascular disease, diseases of bones, kidney and muscles, hypertension, type 2 diabetes mellitus and others (Ahn *et al.*, 2016; Al Mheid & Quyyumi, 2017; Duque *et al.*, 2017; Ekmekcioglu *et al.*, 2017; Field *et al.*, 2013; Gaksch *et al.*, 2017; Grubler *et al.*, 2017; Heaney, 2008; Hill & Aspray, 2017). It seems to have attracted attention in disease prevention due to its key role as a nutritional factor (Sharma *et al.*, 2017).

1,25-Dihydroxyvitamin D [calcitriol, 1,25(OH)2D] is the active form of vitamin D, which binds to its receptor (the vitamin D receptor, VDR) to activate expression of specific genes (Haussler *et al.*, 2013). In humans, inactive vitamin D is converted into 25-hydroxyvitamin D [calcidiol, calcifediol, 25(OH)D] in the liver by CYP2R1 (cytochrome P450 family 2 subfamily R member 1) and then hydroxylated to 1,25(OH)2D in the kidney by 1-α-hydroxylase (CYP27B1). This final step of pro-vitamin D activation is upregulated by the parathyroid hormone (PTH).

Synthesis of vitamin D in the skin requires UV radiation, which can induce DNA damage, preferentially cyclobutane pyrimidine dimers and (6-4)-pyrimidine-pyrimidone photoproducts, which are found in many skin cancers, including melanoma (reviewed in (Pawlowska *et al.*, 2016). Vitamin D protects the skin against UV-induced aging and damage in many pathways that may save it from UV-induced DNA damage and the resulting skin cancer (reviewed in: Piotrowska *et al.*, 2016).

Major functions of the products of genes targeted by 1,25(OH)2D are the absorption of dietary calcium and phosphorus and bone mineralization. Therefore, 1,25(OH)2D is intimately involved in the calcium metabolism. Osteoporosis is likely the most distinctive example of a vitamin D age-related pathology (Gallagher, 2013; Hill & Aspray, 2017; Hill *et al.*, 2013). This inspired us to evaluate the potential of 1,25(OH)2D to slow down or stop the process of aging, or even to reverse it. This issue is closely linked with the role of vitamin D in the pathogenesis and treatment of age-related diseases. The vitamin D receptor is expressed in human retinal pigment epithelium cells as evidenced for ARPE-19 cells (Alsalem *et al.*, 2014). It will be demonstrated that AMD and vitamin D share some common features, e.g. both are associated with aging and the immune system.

VITAMIN D AND AGE-RELATED MACULAR DEGENERATION

Epidemiology

No specific association was found between vitamin D deficiency and AMD in a population of elderly subjects living in Bordeaux, France (Cougnard-Gregoire *et al.*, 2015). Similar results were obtained in a population of Israeli individuals aged over 60 years (Golan *et al.*, 2011). No causal association between vitamin D and early, late and neovascular AMD were observed in a population-based, cross-sectional study enrolling individuals from 7 European countries (McKay *et al.*, 2017). That study also detected no association between 1,25(OH)2D serum levels and polymorphisms in the genes involved in vitamin

D metabolism, including glucocorticoid genes, VDR, CYP2R1 and CYP27B1, and the occurrence of those three forms in AMD. There was no association between vitamin D status and early AMD in the recently published results of the Atherosclerosis Risk in Communities (ARIC), a cross-sectional study enrolling nearly 8,000 Caucasians and 2000 African Americans (Millen *et al.*, 2017).

One large-scale meta-analysis observed a positive correlation between new AMD cases and vitamin D deficiency (Day *et al.*, 2012). As the authors emphasized, this was the first study analyzing the incidence, not the prevalence, of AMD in a vitamin D association study. There is one interesting investigation which examined the association between AMD and vitamin D, i.e. a lower dietary intake of the vitamin was observed in twins with severe AMD than in monozygotic co-twins with less severe AMD (Seddon *et al.*, 2011). That study had an excellent experimental design and revealed an important finding, i.e. vitamin D deficiency might be more strictly associated with the later phases of the disease, when it is especially devastating, rather than with its occurrence. However, vitamin D was not the only factor behind the clinical discordance, since smoking, betaine and methionine intake also contributed to the observed differences. The next important piece of information emerging from that trial is that not only the genetic characteristics, but also the epigenetic profile seems to be important in the development of AMD. However, there were too few subjects enrolled in the trial to permit the elucidation of epigenetic mechanisms in AMD pathogenesis (Blasiak *et al.*, 2013b; Hjelmeland, 2011; Hutchinson *et al.*, 2014; Katoh, 2013; Kwa & Thrimawithana, 2014; Liu *et al.*, 2012). Somewhat in line with that study are results pointing to a lower mean level of 25(OH)D in neovascular AMD than in its non-neovascular counterpart (Itty *et al.*, 2014).

Only a few studies have addressed the anatomical relationships between the changes occurring in the retina in AMD and their association with vitamin D status. It was noted that vitamin D deficiency in older subjects with no clinical signs of AMD was associated with a reduced macular thickness (Graffe *et al.*, 2012). The results of that study may be important from the perspective of AMD diagnosis in its early, preclinical stage. A lower serum concentration of 25(OH)D was observed in wet AMD patients with subretinal fibrosis, suggesting that the vitamin D status could be related to the phenotypical diversity of AMD (Singh, 2014). A trial conducted on a group of older French individuals revealed that a vitamin D deficiency in AMD patients, measured as the 25(OH) D serum concentration, was associated with a decreased thickness of the ganglion cell complex (GCC).

It has been postulated that the effect of vitamin D in the eye might depend on which region is affected by a particular disease (Uro *et al.*, 2015). Furthermore, it has been proposed that the association between serum levels of 25(OH)D might depend on sex, which in turn could be due to differences in the sunlight exposure resulting from different behaviors (Kim *et al.*, 2014). It has been speculated that the 25(OH)D levels could act preventively in late AMD and a similar effect was suspected in diabetic retinopathy, although it seems less likely in case of the dry eye syndrome and cataract.

In a meta-analysis, serum 25(OH)D concentrations below 50 nmol/L were claimed to be associated with late AMD, and conversely, high concentrations were considered to confer protection against AMD (Annweiler *et al.*, 2016). However, there is no consensus about which concentration of vitamin D in the serum can be considered as "normal" and "lower/higher". Moreover, as mentioned, it is not only 25(OH)D in the serum which is important, the intracellular 1,25(OH)2D concentrations should also be taken into account when examining the relationship between vitamin D and the disease.

It has been suggested that high serum concentrations of 25(OH)D can confer protection against early AMD in individuals aged less than 75 years in a population of postmenopausal women (the Carotenoids in Age-Related Eye Disease Study, CAREDS) (Millen *et al.*, 2011). Interestingly, it was documented that vitamin D exerted a protective effect to UV irradiation against neovascular AMD in 481 sibling pairs (Morrison *et al.*, 2011). The serum 25(OH)D concentrations were slightly higher in unaffected individuals than in their AMD-affected counterparts, although that difference was not statistically significant. An evaluation of the metabolome of neovascular AMD patients revealed several unique features as compared to their age-matched controls, including alterations in vitamin D-related metabolites (Osborn *et al.*, 2013).

In summary, some large population-based studies have reported a beneficial effect of vitamin D in AMD prevention, but others have not detected any benefits. It seems that many factors, including ethnicity, dietary habits, genotypes with elevated susceptibility for AMD, and coexisting diseases could be confounding factors.

Diet

There is no consensus about whether there should be dietary recommendations as a way to prevent AMD or to slow down its progression. In general, it seems that early AMD can be accelerated by the intake of fat-rich foods (mono-, trans- or polyunsaturated fatty acids) (Seddon *et al.*, 2003; Seddon *et al.*, 2011) and reduced by a low intake of saturated fat, fish and nuts (Cugati *et al.*, 2007; Wang *et al.*, 2007). The initial large-scale study on how dietary risk factors could influence AMD was conducted in the first National Health and Nutrition Examination Survey (NHANES), which suggested that a diet rich in fruits and vegetables, and its supplementation with vitamins, could reduce the risk of AMD (Goldberg *et al.*, 1988). The conclusion emerging from the third NHANES was that vitamin D might protect against AMD (Parekh *et al.*, 2007). A small-scale population study on AMD in Japan showed that low intakes of n-3 fatty acids, α-tocopherol, zinc, vitamin D, vitamin C, and β-carotene were associated with an increased risk of developing the neovascular form of the disease (Aoki *et al.*, 2016).

Nutritional risk factors for AMD have been assessed in two large-scale trials: AREDS (Age-Related Eye Disease Study) and AREDS2 (Chew, 2017). AREDS revealed that antioxidant vitamins (C, E and β-carotene), zinc and the combination of these vitamins with zinc (AREDS formulation, AREDS supplements) substantially reduced the risk of AMD progression to the late stage in a median 6.5 years follow-up study extended to 10 years (Chew *et al.*, 2014). In addition, AREDS proposed some dietary recommendations to slow down the progression of AMD and these have been confirmed in later studies, including those mentioned above. In AREDS2, β-carotene was replaced with lutein and zeaxanthin, as β-carotene was suspected to cause lung cancer in former smokers (Chew *et al.*, 2012).

In general, despite certain controversial aspects, the subsequent AREDS2 confirmed a positive effect of some of the dietary compounds reported in the previous

study and extended it to some diseases coexisting with AMD, including CVD and impaired cognitive functions (Chew *et al.*, 2012; Chew *et al.*, 2014). It is beyond the scope of this review to discuss all of the interesting aspects emerging from the AREDS/AREDS2 studies, especially since they are still providing some new data and evidence.

Large-scale cohort studies associating AMD with the diet are important if we are to understand better the mechanisms of AMD pathogenesis, and in that way to provide the general population with some reliable and relevant nutritional recommendations. Nonetheless, it should be recognized that they are complicated by many confounding factors, which should be carefully controlled in the study design. For example, the tragedy of β-carotene supplementation and lung cancer shows that not all important aspects of trial design can be anticipated beforehand.

VITAMIN D'S POTENTIAL TO MODULATE AMD RISK FACTORS AND ASSOCIATED STATES

Aging

The final step of vitamin D activation occurs in the kidney (Fig. 2) and this is expected to decrease with age as there is a decline in the general renal function with age (de Jongh *et al.*, 2017; Geraci *et al.*, 2017). It was demonstrated that stimulation with PTH resulted in a substantially reduced production of 1,25(OH)2D in elderly people, in comparison to younger individuals (Kinyamu *et al.*, 1996).

In general, calcium absorption represents the sum of its active transport and passive diffusion (Christakos *et al.*, 2011; Ebeling *et al.*, 1992; Gonzalez Pardo & Russo de Boland, 2013; Sarma & Yang, 2011). Calcium absorption declines with age and this decrease can be associated with a disturbed activity of the calcium transport proteins regulated by 1,25(OH)2D (Christakos *et al.*, 2011; Gonzalez Pardo & Russo de Boland, 2013). Intestinal concentration of VDR can be critical for calcium absorption and a decrease in the numbers of VDRs with age has been observed in humans and experimental animals (de Jongh *et al.*, 2017; Ebeling *et al.*, 1992; Horst *et al.*, 1990; Kinyamu *et al.*, 1996).

1,25-dihydroxyvitamin D also controls an endocrine axis containing the bone-derived hormone FGF23 and the kidney-expressed klotho after association with VDR (Haussler *et al.*, 2012). Such interaction with the involvement of the CYP24A1 and CYP27B1 enzymes, prevents hyperphosphatemia and ectopic calcification, and allows 1,25(OH)2D to maintain mineral integrity of the bones and maintain optimal functions of the kidneys, modulating the aging processes and promoting health span.

The precursor of vitamin D (cholecalciferol) is mainly produced in the skin and requires exposure to UV light. On the other hand, chronic exposure to sunlight can result in premature skin aging – skin photoaging (Kanaki *et al.*, 2016). It has been demonstrated that the production of pro-vitamin D in skin explants decreases with age (MacLaughlin & Holick, 1985). In subsequent studies, it was observed that the vitamin D endocrine system regulated skin aging and furthermore, not only a deficit, but also an overproduction of vitamin D could result in premature skin aging (Reichrath, 2012). There are some controversies surrounding the link between skin aging and vitamin D – there appears to be no correlation between the serum 25(OH)D concentration and facial skin aging (Dawoud *et al.*, 2016).

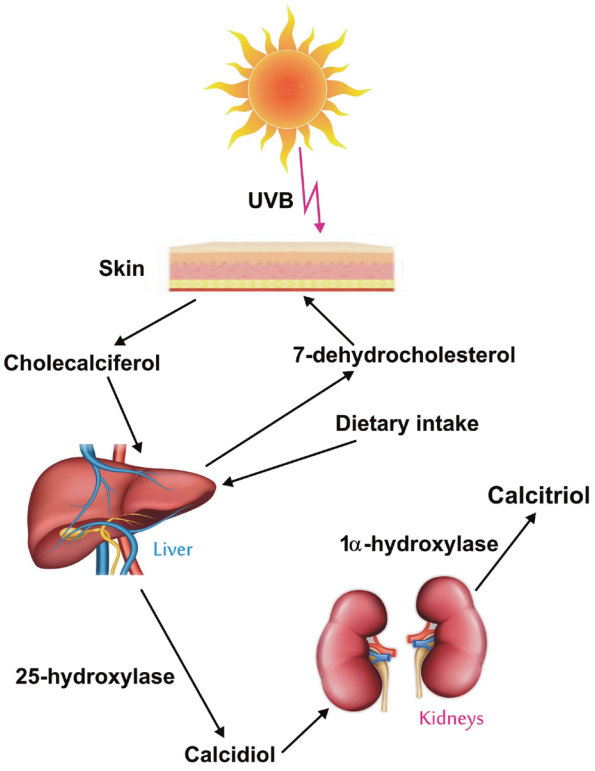

Figure 2. The main steps in the production of active vitamin D that are dependent on aging.
7-dehydrocholesterol, a precursor of vitamin D, is converted to cholecalciferol by solar UVB in the skin. Older people may have an insufficient dietary intake to produce the required amount of 7-dihydrocholesterol and they often suffer from an inadequate exposure to sunlight. Cholecalciferol, which is provitamin D, is converted by liver 25-hydroxylase to calcidiol (25-hydroxyvitamin D), which is transported to the kidney where it serves as a substrate for calcitriol (1,25-dihydroxyvitamin D) production, requiring the involvement of 1α-hydroxylase. This stage is affected by aging as renal function declines in the elderly. The conversion of calcidiol into calcitriol is regulated by the parathyroid hormone, and the activity of this hormone in older people is lower than in the younger population. Calcitriol can be deactivated by sequential C-25 hydroxylation and C-24 ketonization.

Another problem associated with vitamin D metabolism in aging is its deficiency due to either insufficient dietary supply and/or lack of enough exposure to sunlight, both of which are common in the elderly (Need *et al.*, 2008).

In summary, the conversion of vitamin D into its active forms and its role in the cell and organism homeostasis strongly depends on aging (Fig. 2). The disturbance in vitamin D homeostasis in the aging organism raises questions about its role in the pathogenesis of age-related diseases.

Susceptibility genes

Mutations in the genes of the complement system are the most significant genetic factors in the pathogenesis of AMD. It has been demonstrated that two risk alleles for the CFH and CFI genotypes can act synergistically with the vitamin D status, as measured by the serum 25(OH)D levels (Millen *et al.*, 2015; Millen *et al.*, 2011). However, the authors emphasized that they had a relatively small sample size and concluded that the results could be due to chance or residual confounding.

AMD genetic risk factors include variations in the sequence (mutations) and expression of the *HTRA1* (high temperature requirement protein A1) gene located in the 10q26 chromosomal region, which has many single nucleotide polymorphisms (SNPs), creating haplotypes with high susceptibility to AMD (Liao *et al.*, 2017). A reduced expression of HTRA1 has been associated with drusen formation (Pahl *et al.*, 2013). That study was performed on the 10q26-orthologue region of rhesus monkeys; it revealed that the promoter of the *HTRA1* gene contained 9 binding sites for the vitamin D-dependent transcription factor VDR. One of these sites was inactivated by an allele of an SNP present in the HTRA1 promoter, which was associated with drusen formation. An in vitro assay revealed that the drusen risk allele decreased the activity of the HTRA1 promoter after stimulation with 1,25(OH)2D, which was apparently at odds with previously published results. Therefore, not only an increase in the expression of the HTRA1 gene, but also an imbalance in its expression can be associated with an increased risk for developing the AMD drusen phenotype.

The evidence for an association between variations in the AMD susceptibility genes and vitamin D status would be more convincing if a concomitant functional study of the variant of the investigated gene had been performed, as in the studies described above. Moreover, it should be taken into account that expression of a single gene results from interaction of many other gene products.

Inflammation

NLRP3 [NLR (neural retina leucine zipper) family pyrin domain containing 3, NALP3, cryopyrin] is a component of the inflammasome and an important element of the innate immune system. It activates caspase-1 and this leads to subsequent release of interleukin-1α (IL-1α) and IL-18 (He *et al.*, 2016). It is activated by different stimuli, including various pathogens and products of stressed, damaged or dying cells. NLRP3 activation has been associated with pathogenesis of AMD and its role has been linked with autophagy (Celkova *et al.*, 2015; Kauppinen *et al.*, 2016). It was reported that both, 1,25(OH)2D and 25(OH)D had increased the release of IL-1α from human monocytes with this effect being dependent on caspase-1 and NLRP3 (Tulk *et al.*, 2015).

Vitamin D can exert differential effects on the production of pro- and anti-inflammatory cytokines, for example, this vitamin inhibited the release of tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2) and IL-12, as well as interferon-γ (IFN-γ), while it exerted a stimulatory effect on the release of anti-inflammatory cytokines, including IL-4, IL-10 and transforming growth factor-β (TGF-β) (Penna & Adorini, 2000). These and other studies suggest that vitamin D can be considered as an anti-inflammatory agent. Treatment with 1,25(OH)2D has been shown to reduce the corneal inflammatory response to bacterial infection (Kernacki & Berk, 1994).

It was shown that 6 weeks' administration of vitamin D in 12-month aged mice significantly improved indicators of retinal inflammation and aging (Lee *et al.*, 2012). A reduction in amyloid beta accumulation and a decline in the population of retinal macrophages were observed, and these changes correlated with improvements in the animals' visual functions. Therefore, that study provided more evidence of the D potential to protect against the changes associated with AMD and AD.

Emerging evidence suggests that vitamin D is an important regulator of the immune system (see (Wu et al., 2018) for review). However, the exact mechanism of that regulation is not completely known. Vitamin D-metabolizing enzymes and VDR are present in various immunological cells including including monocytes, B and T cells, antigen-presenting cells and others (Prietl *et al.*, 2013). Vitamin D was reported to stimulate differentiation of immune cells, decrease expression of proinflammatory Th1 (IL2, interferon γ, TNFα), but increase antinflammatory Th2 (IL3-5, 10) cytokines (Prietl *et al.*, 2013). It also supports the production of antimicrobial peptides with a decrease in antibody production (Reichrath *et al.*, 2016).

Angiogenesis

Angiogenesis plays a crucial role in the pathogenesis of neovascular AMD; angiogenesis is the formation of new vessels which determines the disease phenotype. This process can be considered as inflammatory angiogenesis, which in contrast to its cancer counterpart, is not a single-cell derived event. However, some results point to the presence of a cross-talk between inflammatory responses at the cellular and molecular levels.

Several studies have highlighted the antiangiogenic potential of vitamin D. Suzuki and coworkers (Suzuki *et al.*, 2000) reported that topical administration of 1,25(OH)2D in mice inhibited corneal neovascularization. These results were confirmed in an *in vitro* experiment using human corneal epithelial cells, suggesting that this vitamin can inhibit production of various cytokines, including IL-1, granulocyte-macrophage colony-stimulating factor, and TNF-α, which can stimulate migration of the Langerhans cells (Suzuki *et al.*, 2000).

Treatment with vitamin D has been also shown to reduce retinal neovascularization in mice with oxygen-induced retinopathy (Albert *et al.*, 2007). These studies revealed that 1,25(OH)2D inhibited morphogenesis in capillary endothelial cells without affecting their migration or proliferation. However, there is one previous report that vitamin D could inhibit migration of endothelial cells (Hisa *et al.*, 1996). Although mechanisms underpinning the neovascularization encountered in cancer and retinopathies need not be identical, there may be some common pathways e.g. it has been suggested that 1,25(OH)2D could inhibit expression of Bcl-2 in retinoblastoma and endothelial cells (Nebbioso *et al.*, 2017; Shokravi *et al.*, 1995).

Retinal cell death

Cell death in the retina occurs in the final stages of several eye disorders, including AMD. However, it is not completely clear how these cells die in AMD (Kaarniranta *et al.*, 2017). In general, retinal cells in AMD can undergo apoptosis or necrosis and furthermore apoptosis can be executed in either a caspase-dependent or an independent pathway (Ferrington *et al.*, 2006). It seems that since several different kinds of cells are present in AMD, i.e. RPE cells, choriocapillaries and neurons, various modes of cell death can occur at any given time, and although it has been extensively investigated, the problem of cell death in AMD is still unresolved.

The basic debate centers on the kind of cell death in AMD, i.e. is it a programmed death or necrosis? As stated above, pure necrosis is rather unlikely as the mechanism of cell death, and instead its programmed version, necroptosis, seems more plausible (Blasiak *et al.*, 2017). Similarly, not only apoptosis, but also a version of apoptosis dependent on caspase-1, designated as pyroptosis, may be involved, especially since this pathway is related

to inflammation (Bergsbaken *et al.*, 2009; Brandstetter *et al.*, 2016). We have proposed that autophagy could be decisive in the choice of cell death mode in AMD (Kaarniranta *et al.*, 2017). In order to assess the protective potential of vitamin D in AMD, its influence on apoptosis, pyroptosis and necroptosis should be explored.

In view of vitamin D's immunoregulatory and anti-inflammatory properties, in general it can be considered as a pro-survival molecule (Chirumbolo *et al.*, 2017). This is due to its role in the stress response mediated through calcium oscillatory signaling to induce autophagy or apoptosis via its modulatory activity to combat calcium overload (Chirumbolo *et al.*, 2017; Wilson *et al.*, 2011). Therefore, because it possesses immunoregulatory properties, vitamin D could induce autophagy instead of a programmed death in AMD-associated stress conditions, and in this way perhaps postpone the induction, or slow down progression of AMD. Vitamin D has been reported to protect human islet cells from apoptosis induced by cytokines through upregulation of A20, which is a zinc finger anti-apoptotic protein (Riachy *et al.*, 2002).

It was shown that administration of a cholecalciferol cholesterol emulsion, a precursor of 1,25(OH)2D, suppressed pyroptosis signaling in an animal experimental model of colitis where infected macrophages were reported to trigger apoptosis (Xiong *et al.*, 2016). If the activity of caspase-8 was inhibited, apoptosis was switched to necroptosis through vitamin D regulation with interconnections to TNF-α and type I IFN (Xu *et al.*, 2014). Therefore, vitamin D can be considered as a compound capable of modulating programmed cell death, justifying its use in research in AMD prevention and therapy.

DNA damage response

Oxidative stress is considered as a primary risk factor for AMD, as well as being involved in conditions encountered in RPE cells associated with AMD as a consequence of exposure to other primary risk factors, e.g. tobacco smoking, consumption of a diet rich in polyunsaturated fatty acids, etc. (Blasiak *et al.*, 2014). This kind of stress is associated with an overproduction of reactive oxygen species (ROS) which are capable of damaging cellular macromolecules, including DNA (Jarrett & Boulton, 2012). Damage to both mitochondrial and nuclear DNA has been considered to play a role in pathogenesis of AMD (Blasiak & Szaflik, 2011; Blasiak *et al.*, 2013a; Ferrington *et al.*, 2016). We and others have demonstrated that AMD patients displayed more evidence of DNA damage and impaired DNA repair, as compared to control individuals without vision disturbances (Hyttinen *et al.*, 2017; Szaflik *et al.*, 2009). There may be changes in the DNA repair capabilities in AMD patients due to mutations in DNA repair genes (Blasiak *et al.*, 2012; Synowiec *et al.*, 2012). However, it is not known whether the increased levels of DNA damage in AMD patients are the reasons or consequences of the disease since both are possible.

DNA damage induces a cascade of events leading to its repair, tolerance or cell death; this is collectively known as the DNA damage response (DDR) (Zhou & Elledge, 2000). Consequently, a difference in the extent of DNA damage between two cells can result not only from a difference in DNA-damaging factors, but also from the cellular reaction to either factor. An increased level of DNA damage in the cell can lead to genomic instability, a characteristic finding in many human disorders. Therefore, integrity of DNA and fidelity of its repair mechanisms are important in AMD prevention and

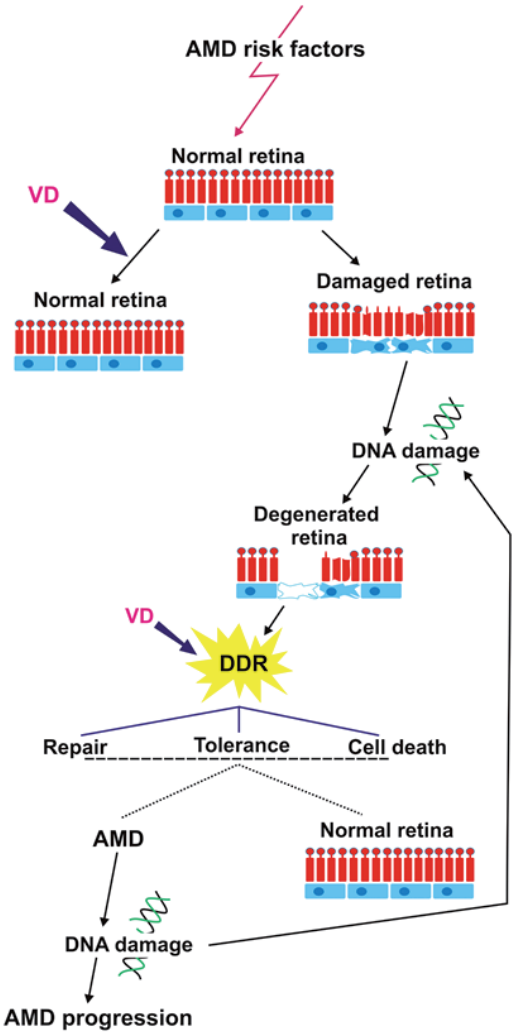

Figure 3. Possible role of vitamin D (VD) in conferring protection against AMD through modulation of DNA damage and DNA damage response (DDR).
Various AMD risk factors can damage both, the nuclear and mitochondrial DNA and these can lead to retinal degeneration. Vitamin D can protect against DNA damage through inactivation of a DNA-damaging factor. DNA damage induces the DNA damage response (DDR), which is a multipathway cellular reaction including many participants, which can be broadly divided into DNA damage repair, its tolerance and cell death. Vitamin D can modulate some of these pathways and thus helps to prevent AMD. However, if AMD has been initiated, then vitamin D may potentiate the existing DNA damage through various mechanisms, including an increase in oxidative stress, a typical occurrence in AMD. This will lead to the accumulation of damaged DNA and hence to AMD progression.

the potential of vitamin D to modulate DDR could also play a role in its properties (Fig. 3).

One of the earliest aspects of DDR is modulation of the cell cycle. 1,25(OH)2D has been shown to increase expression of the p18, p21 and p27 proteins in the head and neck cancer cell line (Gedlicka *et al.*, 2006; Hager *et al.*, 2001; Hager *et al.*, 2004). These proteins are crucial for regulation of the cell cycle and it was observed that the vitamin D induced cell growth inhibition was due to the induction of G0/G1 arrest and this could be associated with an increased expression of p21 (Gedlicka *et al.*, 2006). This increase could be linked with an elevated expression of p53, which is a master regulator of the cell cycle (Maguire & Campbell, 2010) [19]. Another

study demonstrated that 1,25(OH)2D induced arrest at the G1/S checkpoint in the response to mitogens (Shen & Ji, 2015). Therefore, regulation of the cell cycle can be an important mechanism of DDR modulation by vitamin D. However, it should be taken into account that in normal adult retina, the cells do not undergo cycling, i.e. they do not replicate. Retinal neurons are post-mitotic cells and RPE cells are G0 quiescent cells. However, when the RPE cells in the central retina are damaged, they can be replaced by their proliferating counterparts from the periphery (Al-Hussaini *et al.*, 2008). Therefore, DDR with cell cycle regulation is essential for the proper functioning of RPE and the replacement of degraded cells, and failures in these processes have been directly associated with a slow progression of AMD to its final stage.

AMD has been associated with a permanent oxidative stress and ROS overproduction in retinal cells. Oxidative modifications of the DNA bases are the main DNA lesions induced by moderate levels of oxidative stress and 8-oxo-2'-deoxyguanosine (8oxoG) is a marker of DNA oxidation. In general, influence of vitamin D on the level of ROS-induced DNA damage, which is usually evaluated by the level of 8oxoG, suggests that it possesses a protective effect, but the mechanism underlying this action seems to be dependent on many factors, including the kind of cell/tissue and the underlying cellular conditions, as well as the VDR state (Fedirko *et al.*, 2010; Kallay *et al.*, 2002; Mason *et al.*, 2010).

Vitamin D exerts several other effects on the integrity and stability of DNA; these include the induction of apoptosis, as well as the prevention of DNA double-strand breaks and consequent chromosomal aberrations (Chatterjee, 2001). Therefore, vitamin D has the potential to substantially modulate the DDR, and this property can be included into the repertoire of possible ways in which this vitamin can prevent the occurrence and development of AMD. It should be emphasized that impairment of autophagy, which has been linked with AMD, can be considered as a DDR reaction.

Autophagy

Autophagy is a mechanism of cellular internal quality control, i.e. damaged or no longer needed cellular components, including organelles, are degraded in vesicles formed by the fusion of autophagy-specific autophagosomes with lysosomes (Mizushima, 2007). Autophagic degradation can also act against invaders, including viruses and bacteria. Autophagy can occur in three distinct forms: microautophagy, macroautophagy, which here will be subsequently simply called autophagy, and chaperone-mediated autophagy; many proteins are known to be important in its regulation, including about 30 autophagy-related proteins (ATGs), e.g. Beclin-1, mechanistic target of rapamycin (mTOR), the serine/threonine kinase 1 (ULK1), FIP-200, p62 (SQSTM1), microtubule-associated protein light chain 3 (LC3) and others (Blasiak *et al.*, 2014).

Impaired autophagy impacts on the functioning of the RPE cells and is recognized as being crucial in the pathogenesis of many human diseases, including AMD (Chang *et al.*, 2015; Li *et al.*, 2015; Mitter *et al.*, 2012). Its precise role in AMD is not fully understood, but dysfunctional autophagy leads to an increased accumulation of protein aggregates in the RPE cells, resulting from damage to cellular proteins by AMD risk factors (reviewed in: Blasiak *et al.*, 2019). This is supported by the involvement of autophagy in the degradation of used photoreceptor outer segments by the RPE cells (Yu *et al.*, 2018). The photoreceptor segment can be also removed by heterophagy and this process takes place on the apical side of RPE cells, associated with photoreceptor layer (Bosch *et al.*, 1993). This supports the key role of RPE cells in AMD pathogenesis. Another mechanism is thought to involve accumulation of lipofuscin, yellow-brown pigment granules, in aging RPE cells, which are cleared in the lysosome (Kaarniranta *et al.*, 2013). Impaired autophagy reduces efficiency of this process and can contribute to accelerated aging as well as potentiating other risk factors, including oxidative stress, which creates a vicious cycle-like state.

Vitamin D and its analogs can induce autophagy in normal and cancer cells via several mechanisms (Wu & Sun, 2011). Hoyer-Hansen and others (Hoyer-Hansen *et al.*, 2007) demonstrated that autophagy could be induced by an increase in the cytosolic calcium concentration. They also showed that 1,25(OH)2D, as well as its chemotherapeutic analog EB 1089, induced an increase in the calcium level and autophagy in the breast cancer MCF-7 cells. Vitamin D analogs inhibited mTOR activity and induced accumulation of autophagosomes in a process dependent on Beclin-1 and ATG7. Other mediators of this process were Ca^{2+}/calmodulin-dependent kinase kinase-β and AMP-activated protein kinase. Furthermore, the effects of these vitamin D analogs were inhibited by Bcl-2 targeting endoplasmic reticulum.

However, the literature contains conflicting results, suggesting a dual role of calcium ions in autophagy as they can both, stimulate and inhibit this process (Decuypere *et al.*, 2011).

Autophagy is considered as the bridge between the innate and adaptive immunity and vitamin D plays a key role in the immunological response (Shibutani *et al.*, 2015). Consequently, an interrelationship linking this vitamin with autophagy could be observed in a pathogen infection, as such infection can potentially evoke both, the vitamin-D mediated immune response and the triggering of autophagy. For example, human cathelicidin hCAP-18/LL-37, an antimicrobial peptide, was claimed to be a link between vitamin D-dependent immunity and the pathways activated in autophagy (Jee *et al.*, 2016; Yuk & Jo, 2013).

As mentioned above, vitamin D and its receptor signaling play an important role in inflammatory responses (Mangin *et al.*, 2014). As there seems to be a clear connection between inflammation and autophagy, it can be assumed that vitamin D plays a role in the regulation of inflammation through autophagic mechanisms as is the case in inflammatory bowel disease (Suh *et al.*, 2017). The anti-inflammatory autophagy-mediated actions of vitamin D may involve several mechanisms, including inhibition of TNF-α with a concomitant decrease in the Beclin-1 level, recruitment of ATG16, inhibition of IFN-γ.

It has been shown that vitamin D can trigger autophagic death in human myeloid leukemia cells by stimulating binding of Beclin-1 to class III phosphatidylinositol 3-kinase to induce autophagy (Wang *et al.*, 2008). Vitamin D stimulated phosphorylation of the BH3 domain in the pro-apoptotic Bad (Bcl-2-associated death promoter) protein, resulting in disassociation of the Bad/Bcl-xL (B-cell lymphoma-extra large) complex with subsequent inhibition of apoptotic signals. Beclin-1 seems to be critical for these effects, as its knockdown abolished the proautophagic effect of vitamin D.

All of these mechanisms suggest that vitamin D and autophagy can be associated with innate immunity, inflammation, infection and cancer (Wu & Sun, 2011).

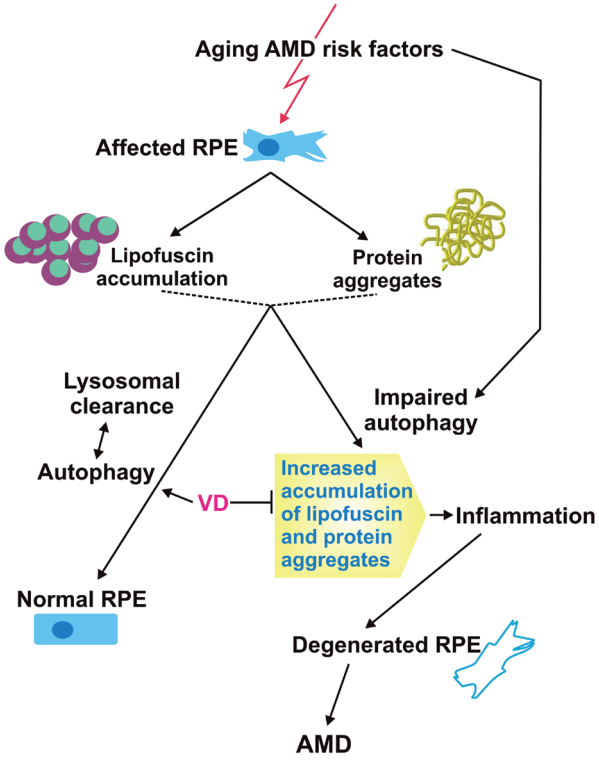

Figure. 4. Autophagy in age-related macular degeneration (AMD) and vitamin D (VD) action.
AMD risk factors, including aging, can induce accumulation of lipofuscin and protein aggregates in retinal pigment epithelium (RPE, represented here by a single RPE cell); these are normally cleared by lysosomal degradation and autophagy, respectively. Autophagy can be impaired by aging and other AMD risk factors, and impaired autophagy can contribute to accelerated aging and potentiate other AMD risk factors, e.g. oxidative stress. Impaired autophagy can also increase accumulation of lipofuscin and protein aggregates, leading to inflammation. Vitamin D has several beneficial properties 1) it can modulate autophagy, 2) it stimulates clearing of lipofuscin and protein aggregates and 3) it directly dampens the inflammatory response

Unfortunately, there is a lack of information relating to vitamin D and autophagy in the retina – the only published study was conducted in the zebrafish eye/retina which was being exploited as a model of polyglutamine-related neurodegenerative disorders (Underwood *et al.*, 2010). However, autophagy is a ubiquitous process, i.e. it is not strictly limited to some specific cells or tissues and therefore its modulation by vitamin D in the eye/retina is possible. Some of the putative relationships between vitamin D and autophagy which have originated from work done in cancer cells need to be interpreted with caution before extrapolating those findings to normal cells, since usually the experiments conducted with cancer cells have required high, non-physiological concentrations of this vitamin in order to obtain an anti-neoplastic effect. Currently, only a putative mechanism of involvement of autophagy in AMD pathogenesis can be considered (Fig. 4).

CONCLUSIONS AND PERSPECTIVES

It is not easy to answer the question posed in the title of this review, as some results on the protective potential of vitamin D in AMD are inconsistent or even contradictory. The most convincing evidence supporting the hypothesis that this vitamin exerts a beneficial effect in AMD originates from its abilities to modulate the immune system, as well as its ability to inhibit inflammation and angiogenesis.

There is no consensus about the precise concentration of vitamin D in the serum, for example, which levels should be considered as "normal" and "lower/higher than normal". However, some kind of consensus seems to be reached and some guidelines can be followed (reviewed in: Pludowski *et al.*, 2013; Pludowski *et al.*, 2018). Still, these guidelines focus mainly on particular aspects on vitamin D metabolism. When the role of this vitamin in bone is considered, the optimal recommended level of 25(OH)D in the serum is 20 ng/mL with daily doses of 400-800 IU, depending on age. When pleiotropic effects of vitamin D are considered, a concentration of 30 ng/mL 25(OH)D and daily doses 400-2000 IU are recommended, depending on age, BMI, health status and ethnicity.

According to various sources, including the Vitamin D Council, the Endocrine Society and the Institute of Medicine, the same concentration of 25(OH)D in the serum can be considered as either a sufficient or a deficient level of the vitamin (Mangin *et al.*, 2014). Therefore, the cut-off value for sufficiency and deficiency of 25(OH)D in the serum should be validated by results from experimental and epidemiological research. This is a serious problem, as these results should be adjusted to an "average individual" level. Autophagy, as a mechanism of cellular action of vitamin D in AMD, seems especially important in the context of this vitamin's preventive potential against AMD, as impaired autophagy has been associated with several critical features of AMD pathogenesis. Impaired autophagy has been implicated in other aspects of AMD pathophysiology, including an impaired DDR and activation of the inflammasome, as autophagy can be involved in both processes (Hyttinen *et al.*, 2017). As vitamin D can play a role in regulation of inflammation through autophagic mechanisms, as shown for the inflammatory bowel disease, it may be also able to influence AMD through an identical or a similar mechanism. Autophagy can lead to protection of AMD-affected retina cells from cell death, but it could also accelerate their demise, and switching between these two effects could be dependent on many factors. Therefore, interconnections between AMD, autophagy and inflammation in the context of the regulatory role of vitamin D in inflammation need to be addressed in further research.

Degeneration of the retina is another important issue to be considered in assessing the potential of vitamin D to modulate AMD. It has been suggested that cellular senescence is a key process contributing to degeneration of retina cells encountered in AMD (Kozlowski, 2015), and we have developed this hypothesis (Blasiak *et al.*, 2017). In the normal adult human eye, the RPE cells of the central retina are quiescent and not able to proliferate due to spatial restrictions. If they are occasionally damaged, they can be replaced by their proliferating counterparts from the periphery (Al-Hussaini *et al.*, 2008). However, if the majority of RPE cells are senescent, the compensating mechanisms can fail and lead to AMD progression. Oxidative stress has been shown to induce senescence in the RPE cells, but the exact mechanism has not been clarified (Aryan *et al.*, 2016). The release of pro-inflammatory cytokines and ROS by senescent cells, DNA damage-induced senescence, induction of senescence in neighboring cells, as well as the interplay between senescence and autophagy are considered to regulate RPE degeneration (Sikora *et al.*, 2014). There-

fore, it would be interesting to examine whether vitamin D can modulate senescence in RPE cells or more extensively in other retinal cells.

In conclusion, there are many pathways through which vitamin D can affect AMD, mainly by modulating effects associated with the disease. Vitamin D has the potential to both, prevent and slow down the progress of AMD, but several issues, including the dose-dependency of this vitamin, its influence on diseases coexisting with AMD, the individual's exposure to sunlight as a factor influencing the activation of this vitamin as well as other risk factors in AMD, need to be addressed before drawing any definite conclusions about the protective role of vitamin D in AMD. It is essential that there should be a resolution of these unanswered questions before it will be possible to issue any dietary recommendations about the dose of vitamin D to be taken by AMD patients.

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Conflicts of Interest

The authors declare no conflict of interest.

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