JOURNAL OF MEDICINAL FOOD
J Med Food 00 (0) 2018, 1–8

DOI: 10.1089/jmf.2017.0130

REVIEW ARTICLE

Sunlight Incidence, Vitamin D Deficiency, and Alzheimer's Disease

Alice Barros Câmara,[1] Iara Dantas de Souza,[1] and Rodrigo Juliani Siqueira Dalmolin[1,2]

[1]*Bioinformatics Multidisciplinary Environment, IMD, Federal University of Rio Grande do Norte, Natal, Brazil.*
[2]*Department of Biochemistry, CB, Federal University of Rio Grande do Norte, Natal, Brazil.*

ABSTRACT Vitamin D (VD) deficiency is a growing problem, affecting a significant portion of the population in many countries. VD deficiency may be related to several diseases, including Alzheimer's disease (AD). This study aimed to review the relationship between VD deficiency and AD. We describe the proteins involved in AD pathogenesis and how those proteins can be influenced by VD deficiency. We also investigated a relationship between AD death rate and solar radiation and we found an increased AD death rate in countries with low sunlight. It was also observed that amyloid precursor protein, ryanodine receptor, mammalian target of rapamycin complex 1, and receptor for advanced glycation end products are associated with a worse prognosis in AD. While the Klotho protein, phosphatase and tensin homologue, and VD receptor are associated with a better prognosis in the disease. The literature suggests that decline in VD concentrations may be involved in the establishment and progression of AD. According to sunlight data, we can conclude that countries with low average sunlight have high AD death rate.

KEYWORDS: • ***Alzheimer's disease rate death*** • ***amyloid precursor protein*** • ***annual sunlight*** • ***neuroprotection***

INTRODUCTION

VITAMIN D (VD) may help protect against cognitive impairment and dementia, in particular, vascular dementia and Alzheimer's disease (AD) by vascular protection, preservation of neurons, and protection against cognitive dysfunction risk factors.[1] VD also exerts protective effects against reactive oxygen species (ROS) and reactive nitrogen species, preventing oxidative damage.[2] VD antioxidant effect could be related to the modulation of antioxidant gene expression. As an example, VD has been described as regulating reducted glutathione levels by an increase in glutamate–cysteine ligase and glutathione reductase expression.[3] In addition, another study suggests that the beneficial effect of calcitriol occurs directly through antioxidant mechanisms instead of gene expression modulation.[4] It is well known that oxidative stress may contribute to the pathophysiology of neurodegenerative diseases leading to behavioral and cognitive function impairment.[1] Genetic analyzes of human genome have pointed the role of several genes in susceptibility to AD, such as genes involved in inflammation and oxidative stress.[5]

VD concentrations above 30 ng/mL are considered normal. VD was considered a neuroprotective factor and concentrations below 16 ng/mL were associated with a high prevalence of AD.[1] Concentrations of VD lower than 20 ng/mL have been observed in Parkinson's and Alzheimer's patients.[6] In addition, subjects with low levels of VD have been described to have worse performance on cognitive tests when compared with people presenting normal VD concentrations.[7]

Experiments using glial cell cultures treated with 1,25-dihydroxyVD3 showed that high vitamin levels were associated with increased mRNA levels of 27 genes, including 17 involved in neurodegenerative and psychiatric diseases or brain morphogenesis. Ten genes among them are responsible for encoding proteins that limit the progression of AD. Therefore, the insufficiency of VD in tissues with low regenerative potential, such as the brain, should be relevant considering the possible damage induced even by moderate VD deficiency.[8]

In a study involving 318 elderly patients, VD deficiency was associated with an increase in brain white matter volume, which is associated with a cognitive decline.[9,10] Some studies do not correlate VD deficiency with cognition deficits and AD.[11,12] However, these studies have evaluated the VD2 supplementation, which is less efficient than VD3. In addition, the cross-sectional studies did not exceed 16 weeks of follow-up, and thus, the biological effects of VD might not be observed during this short period.[13]

VD has shown to stimulate macrophages *in vitro*, increasing clearance of amyloid plaques, the main pathophysiological process in AD. These results suggest that VD plays a key role in reducing the cytotoxicity induced by amyloid plaques.[14] In addition, VD deficiency might lead to alterations in amygdala and hippocampal volumes. The hippocampal neuronal loss is a characteristic of AD and VD treatment could attenuate this atrophy.[1,15] VD also regulates the metabolism of several

Manuscript received 8 October 2017. Revision accepted 5 February 2018.

Address correspondence to: Rodrigo Juliani Siqueira Dalmolin, PhD, Bioinformatics Multidisciplinary Environment, Federal University of Rio Grande do Norte, Rua Odilon Gomes de Lima, 1722, Capim Macio, Natal 59078-400, Brazil, E-mail: rodrigo.dalmolin@imd.ufrn.br

neurotransmitters in the central nervous system, such as acetylcholine, dopamine, serotonin, and gamma aminobutyric acid. Consequently, it is reasonable to think VD influences AD progression at some level.[16]

VD regulates neurotrophin expression, such as nerve growth factor (NGF), neurotrophin 3, and glial-derived neurotrophic factor, as well as survival, development, and neural cell function.[14] NGF has been implicated in maintaining and regulating the normal function of the septohippocampal pathway, which is involved in learning and memory. Furthermore, it has been observed that NGF levels are substantially decreased in AD patients. *In vitro* studies using neuronal cells have demonstrated that NGF negatively modulates amyloid beta precursor protein (*APP*) gene expression, which is involved with amyloid plaque formation.[17] In those studies, increased APP expression was observed after NGF suppression. In addition, calcitriol and VD analogs have been reported to increase AP-1 binding on NGF promoter, which is implicated in NGF expression induction.[17] VD has been suggested as a therapeutic option to prevent cognitive decline and AD. The combined use of VD and docosahexaenoic acid is an emerging strategy to increase the neuron protection against brain lesions. The concomitant use of memantine and VD has also been shown to be effective in slowing cognitive decline. Memantine is useful in the moderate and severe stages of AD, while VD alone only in the early stages of the disease.[17]

There are many works linking VD deficiency and AD. In this study, we extensively review this relationship and pointed proteins that are described as being regulated by VD and as important in AD progression as well. We also access the available data regarding solar incidence and AD death rate in 172 countries. In the following sections, we show the results linking solar incidence and AD death rate and thereafter described the main VD-regulated proteins involved with AD progression.

MATERIALS AND METHODS

Data selection

AD death rate. Data relating to the AD death rate (number of deaths per 100,000 habitants) were obtained from the ''World Life Expectancy'' repository (www.worldlifeexpectancy.com). World life expectancy contains data related to death rate for several diseases in many countries around the world, as well as life expectancy values. Regarding AD death rate, the repository has data from 172 countries (Supplementary Table S1; Supplementary Data are available online at www.liebertonline.com/jmf). All of them were used in the analysis.

Life expectancy. Life expectancy data from the 172 countries were extracted from the ''World Life Expectancy'' repository (www.worldlifeexpectancy.com). Data were provided by the World Health Organization (WHO, 2014), the World Bank, and the United Nations. An average of men and women life expectancy was calculated. Life expectancy at 25 years was considered.

Solar incidence. Data regarding solar incidence were obtained in June 2016 from NASA's Surface Meteorology and Solar Energy project (https://eosweb.larc.nasa.gov/cgi-bin/sse/grid.cgi). The geographical coordinates of the five most populous cities of each country were collected, and then, the solar incidence was retrieved for each city. The annual solar incidence of a country was obtained by the average annual solar incidence of the five most populous cities in the country.

Statistical analyses. Statistical analyses were performed using the R language. For statistical analyses, the Wilcoxon–Mann–Whitney test was used. Values of $P < .05$ were considered significant.

RESULTS

Solar incidence and AD

Experimental studies involving VD and AD are rare, usually restricted to a group of patients at a given location.[14,17–22] The average concentration of VD is not known in many countries, making difficult an epidemiological analysis in large scale. In the absence of large-scale available data about serum VD concentrations in patients with AD, we investigated the relationship between AD death rate and the average annual solar incidence of 172 countries for which data were available (Supplementary Table S1). Solar incidence ranges from 2.12 kWh/m^2/day in Iceland to 6.37 kWh/m2/day in Niger. The distribution midpoint (4.25 kWh/m^2/day) was used to classify the countries into two groups: those with the average solar incidence above the midpoint (high-incidence group, containing 129 countries) and those with the average solar incidence below the midpoint (low-incidence group, containing 43 countries). According to Figure 1a, countries with high solar incidence have significantly lower AD death rate (4.47 deaths/100,000 habitants in average) than countries with low solar incidence (12.34 deaths/100,000 habitants in average).

Since AD is prevalent in elderly people, we evaluated the life expectancy of the 172 countries analyzed (Supplementary Fig. S1) to evaluate if AD death rate could be biased by life expectancy. In fact, countries with high solar incidence have lower life expectancy than countries with low solar incidence (Supplementary Fig. S1a) and all evaluated countries with life expectancy below 75 years have AD death rate less than 10 deaths per 100,000 habitants (Supplementary Fig. S1b). We then analyzed the subgroup of countries with life expectancy equal or greater than 75 years (90 countries in total). Figure 1b shows that low solar incidence countries have significantly greater AD deaths rate when compared with high solar incidence countries, even when low life expectancy countries are excluded from the analysis.

Although the data presented here do not confirm the relationship between VD deficiency and AD, it can be interpreted as an indicative of this relationship, since solar incidence affects directly the synthesis of VD3.[23–27] Hypovitaminosis D usually reflects a reduced sun exposure. This condition must be treated with an adequate exposure to solar radiation instead

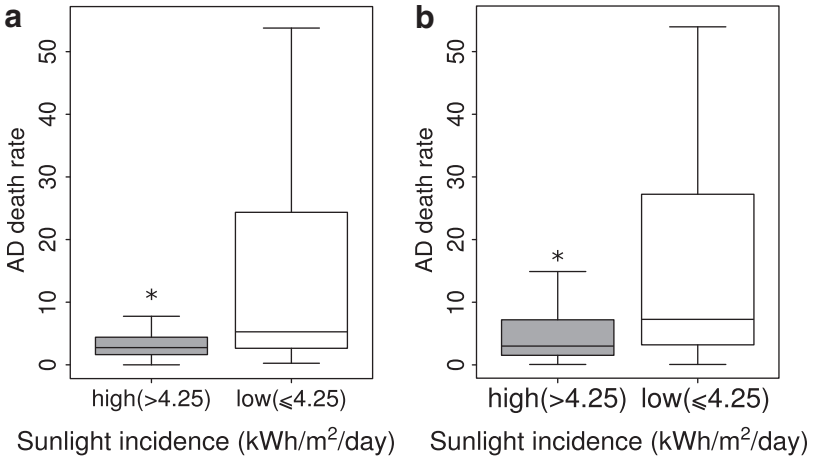

FIG. 1. AD death rates in countries with high and low sunlight incidence. Distribution of AD death rates per 100,000 habitants in countries with average annual solar incidence greater than 4.25 kWh/m^2/day (*high*) and equal or lower than 4.25 kWh/m^2/day (*low*): **(a)** all 172 countries present at World Life Expectancy repository (129 countries in high group and 43 countries in low group); **(b)** the 90 countries presenting life expectancy equal or greater than 75 years (55 countries in high group and 35 countries in low group). Boxes represent the IQR, the line inside it represents the median, and the *bottom* and *top lines* of the *box* are the first and the third quartiles, respectively. *Whiskers* limits are the lowest and the highest observation within 1.5 of IQR from the lower and upper quartiles. *$P < .05$ (Wilcoxon–Mann–Whitney test) when comparing to respective low group. Statistics and graphs were generated using R language. IQR, interquartile range; AD, Alzheimer's disease.

of exogenous supplements.[27] According to Krzywanski *et al.*, sun exposure proves to be more efficient in VD acquisition than oral supplementation. Proximity to the equator line is a strong stimulus for VD synthesis since efficiency in VD production increases in high ultraviolet B radiation.[25] Supplementation with VD2 (obtained by foods) is described to be less efficient than supplementation with VD3 (obtained by ultraviolet radiation).[13] In addition, the relationship between VD receptor (VDR) and VD concentration may be influenced by sun exposure but not by dietary intake of VD.[26]

Proteins associated with VD deficiency and AD

Several proteins are known to be involved with AD pathophysiological processes (Fig. 2a). Other proteins are described as having neuroprotective effect on AD (Fig. 2b), improving the prognosis and/or reducing the damage caused by the disease. Some of the proteins involved with AD are directly or indirectly regulated by VD (Table 1). Among the proteins known to be involved in AD progression, one of the most important is APP. APP (also known as Aβ protein) is a

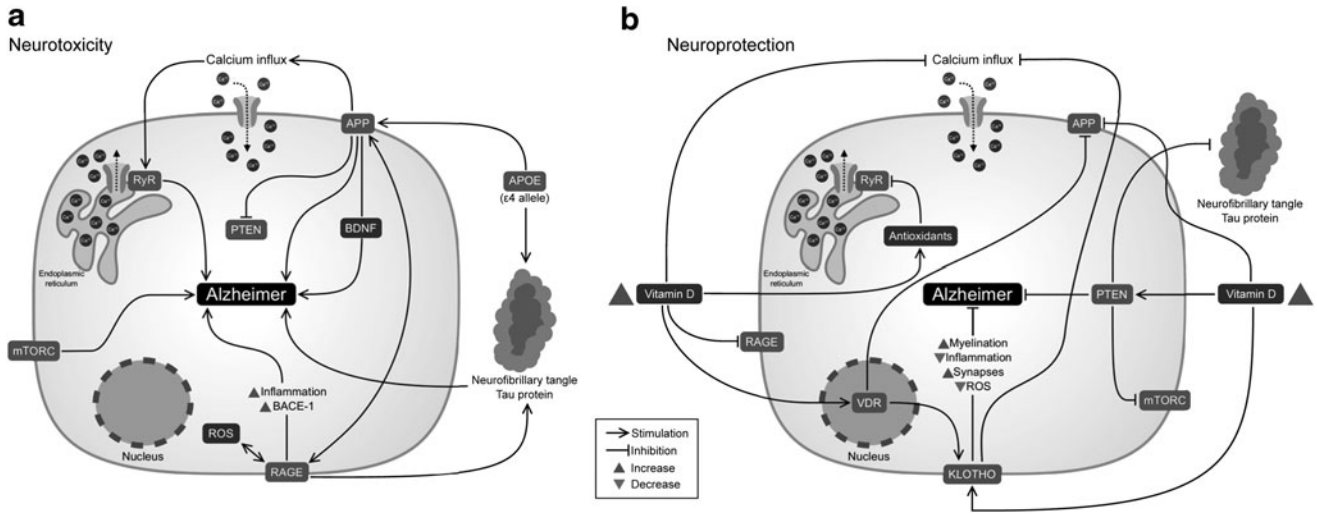

FIG. 2. Proteins associated with VD and AD. Proteins related to AD are shown according to their neurotoxic **(a)** or neuroprotective **(b)** role in AD. APP is directly involved with AD neurotoxicity. APP is involved in reducing BDNF levels, disrupts PTEN signaling and calcium homeostasis. The ε4 APO E allele contributes to APP deposition and neurofibrillary tangle formation. APP and RAGE exert a positive feedback on their own expression. RAGE is indirectly involved with neurofibrillary tangle formation and stimulates BACE-1 and neuroinflammation, which are indirectly related to AD. RAGE is activated by ROS and also increases oxidative stress. RyR and mTORC are involved with neurotoxicity in AD. The increased calcium influx sensitizes RyR. VD is able to suppress *RAGE* and *APP* expression and is indirectly associated with antioxidant synthesis calcium influx. Klotho is able to reduce ROS and inflammation, to reduce calcium influx, and to have a beneficial role in synapses and myelination. VD and VDR stimulate Klotho synthesis and VDR suppresses APP. VD enhances *PTEN* expression, PTEN inhibits mTORC and decreases TAU aggregates, playing a neuroprotective role in AD. Elements in the figure are not showed in real scale. ROS, reactive oxygen species; VD, vitamin D; APP, amyloid beta precursor protein; VDR, vitamin D receptor; RyR, ryanodine receptor; PTEN, phosphatase and tensin homologue; RAGE, receptor for advanced glycation end products; BACE-1, β-site amyloid protein cleavage enzyme 1; BDNF, brain-derived neurotrophic factor; APOE, apolipoprotein E.

Table 1. Effects of Vitamin D on Proteins Related to the Pathogenesis of Alzheimer's Disease

Protein	*Role in AD*	*VD as a regulator*
Neurotoxicity		
APP	Constitutes the amyloid plaques.[28] Decreases BDNF levels.[30–32] Disrupts PTEN signaling and calcium homeostasis.[30,31,51] Exerts a positive feedback on *RAGE* expression.[71] Associated with neurodegeneration and cytotoxicity.[71] Suppresses *VDR* expression.[71]	Stimulates Aβ peptide phagocytosis and suppresses APP expression.[30]
mTORC	Involved with AD through unclear mechanisms.[42]	Inhibits mTORC1.[42]
RAGE	Stimulates BACE-156 and neuroinflammation.[31,42,61] Exerts a positive feedback on APP expression.[62] Regulates APP transport.[57] Involved with neurofibrillary tangle formation, synaptic transmission deficit, and neurodegeneration.[57] Increases oxidative stress.[42,57,61]	Suppresses *RAGE* expression.[63–66]
RyR	Associated with memory loss and age-related cognition decline.[42]	Indirectly prevents RyR sensitization.[42]
Neuroprotection		
Klotho	Reduces ROS and inflammation.[31,42,43] Reduces calcium influx.[42] Associated with antioxidant synthesis, reasoning, memory, and cognition.[31,44] Exerts a beneficial role in synapses and myelination.[43,46] Indirectly regulates the activity of mTORC1.[42,49]	Stimulates *KLOTHO* expression.[45]
PTEN	Inhibits mTORC.[42] Decreases TAU aggregates.[53]	Increases *PTEN* expression.[42,52]
VDR	Stimulates Klotho synthesis.[45] Suppresses *APP* gene transcription.[70] Interacts with SMAD3.[33]	Increases *VDR* expression.[30] Suppresses *APP* transcription.[70]

AD, Alzheimer's disease; ROS, reactive oxygen species; VD, vitamin D; APP, amyloid beta precursor protein; VDR, vitamin D receptor; BDNF, brain-derived neurotrophic factor; RyR, ryanodine receptor; mTORC1, mammalian target of rapamycin complex 1; PTEN, phosphatase and tensin homologue; RAGE, receptor for advanced glycation end products; BACE, β-site amyloid protein cleavage enzyme.

transmembrane protein that is cleaved to form Ap oligomers (amyloid peptides). These fragments form the protein base of the amyloid plaques found in AD patients.[28] The biological functions of this protein have been investigated for many years and believed that APP is involved in synaptic and cellular adhesion, axonal degeneration and inhibition, intracellular signaling, apoptosis, among others. In addition, a body of evidence suggests a trophic function of APP in neurons and synapses.[29] APP fragments are intimately involved with events that lead to progressive neurodegeneration in AD. Toxicity of Ap monomers leads to calcium homeostasis disturbance and changes in brain-derived neurotrophic factor (BDNF) levels (Fig. 2a), affecting the well functioning of neurons and their synapses.[30,31] Low levels of BDNF are found in Alzheimer's patients.[32]

Dysregulation in amyloid metabolism, such as APP clearance decrease and/or APP overproduction, is described as the most important molecular event leading to AD pathology and symptoms. An important risk factor for AD is the ε4 allele of apolipoprotein E (Apo E).[33] The ε4 allele contributes to amyloid protein deposition. Currently, two models seek to explain the role of Apo E in APP accumulation. The first consists in endocytosis of soluble APP and Apo E associated with a lipid particle followed by APP aggregation in amyloid fibrils, which are released into the extracellular environment. The second justifies increased APP production through cellular cholesterol increase. The cholesterol deposition in cellular membranes contributes to Aβ protein synthesis.[34] The ε4 allele of Apo E is associated with neurofibrillary tangles, amyloid proteins, phosphorylated TAU protein, and accelerated memory decline.[35]

Experimental data showed that VD deficiency contributes to APP accumulation, reducing the protection against cognitive decline, contributing to poor performance in tasks related to memory and learning, and suppressing the hippocampal synaptic plasticity. Human studies showed that individuals with high concentrations of VD have low amounts of APP, regardless of gender, age, family history, and concentrations of Apo E. Treatment with VD can stimulate Aβ peptide phagocytosis, suppress APP gene transcription, and Aβ oligomer synthesis, controlling the inflammatory process and increasing the *VDR* expression.[30]

In addition to the amyloid precursor protein, the ryanodine receptor (RyR) is also associated with AD progression (Fig. 2a). RyR is a family (RyR1, RyR2, and RyR3) of ion channels known to be responsible for calcium release from intracellular reserves during striated muscle contraction. RyR might be regulated by several proteins, ions, as well as redox modifications. RyR3 is the brain isoform expressed in the hippocampus, thalamus, Purkinje cells, and striatum, and is related to synaptic transmission and plasticity.[36] RyR 1 and RyR 2 are also found in the brain, although they are not predominantly present in the nervous system.[37] The

increased calcium influx through L-type calcium channels sensitizes RyR, which is associated with memory loss and age-related cognition decline. Antioxidants prevent a decline in cognition, long-term depolarization, and memory loss by preventing the RyR sensitization. In this way, VD is important for the indirect synthesis of antioxidant enzymes and thus in AD prevention.[1,3,38–41] In addition, VD decreases calcium influx through L-type calcium channels, preventing RyR sensitization. Aβ oligomers are responsible for increasing intracellular calcium concentration, contributing to memory loss by inducing long-term depolarization and by activating RyR. Dantrolene sodium, a drug used in AD treatment, inhibits RyR by reducing the intracellular calcium. Klotho is also involved with intracellular calcium uptake reduction, preventing the forgetfulness of AD.[42]

The transmembrane protein Klotho is present in cerebrospinal fluid and is known to be expressed in the brain choroid plexus, parathyroid glands, and kidney tubular cells.[43] Klotho is associated with antioxidant synthesis, reasoning, memory, and cognition.[31,44] In addition, Klotho increases the expression of peroxiredoxins (Prx-2, Prx-3) and thioredoxin reductase 1, which act together to reduce ROS.[42] Klotho gene transcription is stimulated by VD through interaction with VDR and retinoid X receptor (RXR) (Fig. 2b). Klotho deficiency is related to aging, early death, weight loss, infertility, calcified arteries, atherosclerosis, emphysema, skin atrophy, and osteoporosis.[45] The protein is found in low concentrations in women when compared with man, elderly people, VD deficients, and Alzheimer's patients.[43] Klotho synthesis decreases with aging and overexpression is associated with a longer life. Studies have associated Klotho deficiency with increased lipid peroxidation and hippocampal DNA damage in mice, leading to cognitive decline, aging, and cerebral pathology.[43]

Klotho plays an important role in brain myelination and synapses at the hippocampus and frontal cortex.[43,46] Another suggested role of Klotho is a protective effect on inflammation by suppressing TNF-α expression and attenuation of NF-κB activation and IkB phosphorylation.[31] Experiments have reported that Klotho deficiency is involved in cyclooxygenase 2 (COX-2) overexpression.[47] COX may be involved in neurodegenerative mechanisms, and administration of nonsteroidal anti-inflammatory drugs might reduce AD risk. In fact, COX2 is involved with APP deposition and is found to be increased in areas related to memory in AD patients.[48] The importance of Klotho in synapses, antioxidant synthesis, protective effect on inflammation, and protection of neuronal myelin may point that protein as central in AD.

Mammalian target of rapamycin complex 1 (mTORC1) is a complex regulated by insulin pathway, formed by the proteins LST8, KOG1, TCO89, TOR1, PRAS40, and DEPTOR. It is known that Klotho indirectly regulates the activity of mTORC1 by inhibiting the insulin signaling pathway.[42,49] mTORC1 controls cell growth through signaling pathways that respond to nutritional integration signals, such as availability of amino acids. mTORC1 is also involved in cell life, environmental stress response, and autophagy.[49] Increase in mTORC1 signaling pathways is associated with aging, AD, cancer, and type 2 diabetes. The exact mechanisms by which the mTORC1 complex influences AD are not understood. However, it is known that VD inhibits mTORC1 and increases the expression of phosphatase and tensin homolog (PTEN) transcript 4, which also inhibits mTORC activity (Fig. 2a).[42]

PTEN is an intracellular protein present in low concentrations in AD patients. PTEN is important for cell survival and growth, participating in several cell-signaling pathways. PTEN has a lipid phosphatase activity that modulates cell cycle progression, inhibits cell migration, and integrin-mediated cell spreading. PTEN plays a key role in AKT-mTOR signaling pathway, controlling the integration process of newly developed neurons during adult neurogenesis.[50] Researches provide evidences that Aβ oligomers disrupt PTEN signaling, which might lead to loss of synapses.[51] VD enhances *PTEN* expression through the VD receptor and thereby prevents AD progression (Fig. 2b).[42,52] PTEN can be inhibited in VD deficiency, impairing cellular functions and neuronal survival, playing a neuroprotective role in AD. PTEN has been described to affect TAU phosphorylation, aggregation, and association with microtubules. Significant PTEN loss in AD patient brains has been correlated with increased phospho-tau at Ser-214 concentration.[53]

The receptor for advanced glycation end products (RAGE) is also associated with AD progression. RAGE is a member of cell surface immunoglobulin families, described as a signal transduction receptor for nonenzymatic glycation end products and is considered a proinflammatory receptor.[54] Advanced glycation end products (AGEs), generated by hyperglycemia and/or oxidative stress, can mediate inflammatory cell activation through RAGE. It can result in hypoxia, ischemia, and arterial lesion.[55] There is an increasing body of evidence of AGE involvement in neurodegenerative processes, including AD. RAGE may be involved in Ap monomer aggregation. Experiments suggested that RAGE can bind to Aβ42 protein and regulates its transport across the blood/brain barrier.[56] This receptor is involved in amyloid protein production and accumulation, neurofibrillary tangle formation, synaptic transmission deficit, and neurodegeneration. RAGE contributes to Aβ protein synthesis by increasing inflammatory response and oxidative stress.[57]

Aβ oligomers activate RAGE when ROS are generated (Fig. 2a). RAGE activation can result in neuroinflammation, neurodegeneration, and memory loss. It is also known that RAGE increases oxidative stress by NADPH oxidase activation.[42] RAGE is involved in TAU hyperphosphorylation, a phenomenon observed in AD.[57–59] TAU phosphorylation allows proteins to bind together and form tangled threads.[60] Treatment with hesperidin can suppress oxidative stress and inflammation through RAGE inhibition, conferring neuroprotection.[61]

The G8S2 polymorphism of the RAGE receptor encoding gene is also associated with AD and this polymorphism increases AD risk. G8S2 polymorphism may contribute to Aβ protein production and its accumulation in the brain since the single nucleotide polymorphism (SNP) is located in an exon that may be involved in signaling change responsible for accelerating amyloid protein processing. In

addition, RAGE activation stimulates β-site amyloid protein cleavage enzyme 1 expression, which is important for Aβ protein production (Fig. 2a). The amyloid protein and RAGE can exert a positive feedback on their own production and expression. The G8S2 polymorphism may also be responsible for increasing Aβ protein transport in the brain.[62]

Deletion of *RAGE* gene has been described to decrease intracellular Aβ levels. This deletion decreases mitochondrial dysfunction in cortical neurons in culture.[62] RAGE inhibition is also involved with the reduction of inflammatory cell migration and proliferation.[55] VD treatment was able to reduce *RAGE* expression in cell line experiments and decrease *RAGE* expression in diabetic rats.[63–66]

Finally, VD receptor is associated with a neuroprotective effect in AD, improving the prognosis (Fig. 2b). VDR is the only high-affinity receptor to VD and it is the main mediator for VD actions. The genomic and nongenomic actions of VD are mediated by nuclear and membrane receptors, respectively, and the VDR is identical in both locations. It has been proposed that *VDR* may use alternative mechanisms to interact with genomic DNA. These alternative mechanisms can explain some of the specific cellular actions of VDR, as well the repressive functions on gene transcription.[17,67] In the human brain, *VDR* is expressed mainly in the hypothalamus, thalamus, hippocampus, dentate gyrus, substantia nigra, and cortex, both in neurons and astrocytes. VD has several functions in the brain, such as cell proliferation, differentiation, and apoptosis, and it can contribute to a neuroprotective effect.[14,17,64,68] Experiments with mice showed that they could not survive without VD receptors.[69]

Polymorphisms in VD receptor have been described as risk factors for AD by impairing learning and memory. These polymorphisms deregulate calcium and redox signaling pathways and increase calcium influx.[42] *VDR* polymorphisms may also decrease VD affinity to the receptor, affecting neurotrophin expression, which may lead to aging and neuronal death.[17] In fact, an increase in *VDR* polymorphisms was found in Alzheimer's brains and a decrease in *VDR* mRNA levels was reported in hippocampus affected by AD.[1] Polymorphisms in the *VDR* gene promoter 5′ region affect mRNA expression, whereas in the 3′ untranslated region affect mRNA stability. The ''A'' allele of the Apal *VDR* polymorphism has been suggested as a risk allele to AD. Another risk allele is the ''T'' allele, of the Taql polymorphism.[22] Another *VDR* polymorphism associated with AD corresponds to the CDX2 allele polymorphism (SNP CDX2), which results in decreased VD receptor activity and increased Aβ protein expression.[70] These polymorphisms may be associated with changes in translation efficiency and mRNA stability.[22]

In vitro experiments showed that *VDR* overexpression or VD treatment suppresses *APP* transcription in neuroblastoma cells.[70] In addition, amyloid protein can trigger neurodegeneration and cytotoxicity by suppressing the *VDR* expression.[71] VDR interacts with SMAD 3 protein, which is involved in Aβ protein processing through TGF-β signaling. Finally, VDR inhibition may result in neurotoxic effects, cognitive and behavioral deficits, premature aging, decreased life expectancy, and calcium homeostasis dysregulation.[17]

DISCUSSION

According to the literature, VD deficiency may be involved in the establishment and progression of AD. The amyloid protein is an important component of the disease; however, the complexity of AD suggests the involvement of other proteins in the pathology. The amyloid precursor protein, *RyR*, *mTORC 1*, and *RAGE* are associated with worse prognosis in AD, while *Klotho*, *PTEN*, and *VDR* are associated with better AD prognosis. Aβ oligomers might be involved in the synthesis, activation, or inhibition of those proteins, participating directly and indirectly in AD establishment and progression.

The role of VD in AD prevention is reinforced by sunlight data. We clearly demonstrated that countries with low sunlight incidence have greater AD death rate when compared with sunny countries. It is not clear how VD varies according to changes in solar ultraviolet radiation. A recent cohort study has been proposed to evaluate seasonal VD variation in Australians; unfortunately, the results are not yet available.[72] The greater life expectancy in countries with low sunlight incidence could be an important biasing factor since AD incidence increases with age. However, AD is not an inevitable result of aging and the disease onset ranges from 40 to 90 years of age.[73] The usual onset is 65 years of age and the outcome ranges from 3 to 9 years after diagnosis.[74] Accordingly, we identified increased AD in low sunlight countries even considering only countries with a life expectancy greater than 75 years. Besides life expectancy, it would be crucial to evaluate other population parameters such as ethnicity since countries largely vary according to ethnicity homogeneity. However, to our knowledge, there are no organized data regarding this information.

Taken together, information discussed here suggests that VD deficiency is involved with AD progression, despite not necessarily triggering the pathology. New studies will be required to establish the relationship between VD deficiency and AD progression, such as cohort studies and studies including VD3 dosage. Data integration involving transcriptional and genomic data in combination with VD measurement in long-term experiments certainly will shed a light on VD role in AD.

ACKNOWLEDGMENTS

We acknowledge World Life Expectancy's repository and NASA's Surface Meteorology and Solar Energy project for providing public access to their data. This work has been financed by the governmental Brazilian agency National Council for Scientific and Technological Development (CNPq, Portuguese: *Conselho Nacional de Desenvolvimento Científico e Tecnológico*), grant 444856/2014-5. The scholarships were financed by governmental Brazilian agency Coordination for the Improvement of Higher Education Personnel (CAPES, Portuguese: *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*).

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

REFERENCES

1. Buell JS, Dawson-Hughes B: Vitamin D and neurocognitive dysfunction: Preventing ''D''ecline? Mol Aspects Med 2008;29: 415–422.
2. Garcion E, Nataf S, Berod A, Darcy F, Brachet P: 1,25-Dihydroxyvitamin D3 inhibits the expression of inducible nitric oxide synthase in rat central nervous system during experimental allergic encephalomyelitis. Mol Brain Res 1997;45:255–267.
3. Jain SK, Micinski D: Vitamin D upregulates glutamate cysteine ligase and glutathione reductase, and GSH formation, and decreases ROS and MCP-1 and IL-8 secretion in high-glucose exposed U937 monocytes. Biochem Biophys Res Commun 2013;437:7–11.
4. Longoni A, Kolling J, Siebert C, *et al.*: 1,25-Dihydroxyvitamin D3 prevents deleterious effects of homocysteine on mitochondrial function and redox status in heart slices. Nutr Res 2017;38: 52–63.
5. Serretti A, Olgiati P, De Ronchi D: Genetics of Alzheimer's disease. A rapidly evolving field. J Alzheimers Dis 2007;12:73–92.
6. Thacher TD, Clarke BL: Vitamin D insufficiency. Mayo Clin Proc 2011;86:50–60.
7. Tanik N, Balbaloğlu Ö, Ucar M, *et al.*: Does vitamin D deficiency trigger carpal tunnel syndrome? J Back Musculoskelet Rehabil 2016;29:835–839.
8. Nissou M-F, Brocard J, El Atifi M, *et al.*: The transcriptomic response of mixed neuron-glial cell cultures to 1,25-dihydroxyvitamin d3 includes genes limiting the progression of neurodegenerative diseases. J Alzheimers Dis 2013;35:553–564.
9. Valenzuela MJ, Sachdev P: Magnetic resonance spectroscopy in AD. Neurology 2001;56:592–598.
10. Sakurai T, Ogama N, Toba K: Lower vitamin D is associated with white matter hyperintensity in elderly women with Alzheimer's disease and amnestic mild cognitive impairment. J Am Geriatr Soc 2014;62:1993–1994.
11. Stein MS, Scherer SC, Ladd KS, Harrison LC: A randomized controlled trial of high-dose vitamin D2 followed by intranasal insulin in Alzheimer's disease. J Alzheimers Dis 2011;26:477–484.
12. Przybelski R, Agrawal S, Krueger D, Engelke JA, Walbrun F, Binkley N: Rapid correction of low vitamin D status in nursing home residents. Osteoporos Int 2008;19:1621–1628.
13. Pepper K, Judd S, Nanes M, Tangpricha V: Evaluation of vitamin D repletion regimens to correct vitamin D status in adults. Endocr Pract 2009;15:95–103.
14. Littlejohns TJ, Henley WE, Lang IA, *et al.*: Vitamin D and the risk of dementia and Alzheimer disease. Neurology 2014;83:920–928.
15. Wegler C, Wikvall K, Norlin M: Effects of osteoporosis-inducing drugs on vitamin D-related gene transcription and mineralization in MG-63 and Saos-2 cells. Basic Clin Pharmacol Toxicol 2016; 119:436–442.
16. Booth DR, Ding N, Parnell GP, *et al.*: Cistromic and genetic evidence that the vitamin D receptor mediates susceptibility to latitude-dependent autoimmune diseases. Genes Immun 2016;17: 213–219.
17. Banerjee A, Khemka VK, Ganguly A, Roy D, Ganguly U, Chakrabarti S: Vitamin D and Alzheimer's disease: Neurocognition to therapeutics. Int J Alzheimers Dis 2015;2015:192747.
18. Lemire P, Brangier A, Beaudenon M, Duval GT, Annweiler C: Cognitive changes under memantine according to vitamin D status in Alzheimer patients: An exposed/unexposed cohort pilot study. J Steroid Biochem Mol Biol 2018;175:151–156.
19. Mokry LE, Ross S, Morris JA, Manousaki D, Forgetta V, Richards JB: Genetically decreased vitamin D and risk of Alzheimer disease. Neurology 2016;87:2567–2574.
20. Dursun E, Alaylıoğlu M, Bilgiç B, *et al.*: Vitamin D deficiency might pose a greater risk for ApoEε4 non-carrier Alzheimer's disease patients. Neurol Sci 2016;37:1633–1643.
21. Chaves M, Toral A, Bisonni A, *et al.*: Treatment with vitamin D and slowing of progression to severe stage of Alzheimer's disease. Vertex 2014;25:85–91.
22. Łaczmański Ł, Jakubik M, Bednarek-Tupikowska G, Rymaszewska J, Słoka N, Lwow F: Vitamin D receptor gene polymorphisms in Alzheimer's disease patients. Exp Gerontol 2015;69:142–147.
23. Castro LCG de: The vitamin D endocrine system. Arq Bras Endocrinol Metabol 2011;55:566–575.
24. Webb AR, Aseem S, Kift RC, Rhodes LE, Farrar MD: Target the message: A qualitative study exploring knowledge and cultural attitudes to sunlight and vitamin D in Greater Manchester, U.K. Br J Dermatol 2016;175:1401–1403.
25. Krzywanski J, Mikulski T, Krysztofiak H, Mlynczak M, Gaczynska E, Ziemba A: Seasonal Vitamin D status in polish elite athletes in relation to sun exposure and oral supplementation. PLoS One 2016;11:e0164395.
26. Livingstone KM, Celis-Morales C, Hoeller U, *et al.*: Weekday sunlight exposure, but not vitamin D intake, influences the association between vitamin D receptor genotype and circulating concentration 25-hydroxyvitamin D in a pan-European population: The Food4Me study. Mol Nutr Food Res 2017;61: 1600476.
27. Razzaque MS: Sunlight exposure: Do health benefits outweigh harm? J Steroid Biochem Mol Biol 2018;175:44–48.
28. O'Brien RJ, Wong PC: Amyloid precursor protein processing and Alzheimer's disease. Annu Rev Neurosci 2011;34:185–204.
29. Muller UC, Zheng H: Physiological functions of APP family proteins. Cold Spring Harb Perspect Med 2012;2:a006288–a006288.
30. Keeney JT, Butterfield DA: Vitamin D deficiency and Alzheimer disease: Common links. Neurobiol Dis 2015;84:84–98.
31. Abraham CR, Chen C, Cuny GD, Glicksman MA, Zeldich E: Small-molecule Klotho enhancers as novel treatment of neurodegeneration. Future Med Chem 2012;4:1671–1679.
32. Mattson MP, Magnus T: Ageing and neuronal vulnerability. Nat Rev Neurosci 2006;7:278–294.
33. Jack CR, Albert MS, Knopman DS, *et al.*: Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement 2011;7:257–262.
34. Ojopi EPB, Bertoncini AB, Dias Neto E: Apolipoproteína E e a doença de Alzheimer. Arch Clin Psychiatry (São Paulo) 2004;31: 26–33.
35. Caselli RJ, Reiman EM: Characterizing the preclinical stages of Alzheimer's disease and the prospect of presymptomatic intervention. J Alzheimers Dis 2013;33 Suppl 1:S405–S416.
36. Lanner JT, Georgiou DK, Joshi AD, Hamilton SL: Ryanodine receptors: Structure, expression, molecular details, and function in calcium release. Cold Spring Harb Perspect Biol 2010;2: a003996–a003996.

37. Franzini-Armstrong C, Protasi F: Ryanodine receptors of striated muscles: A complex channel capable of multiple interactions. Physiol Rev 1997;77:699–729.
38. Lin AMY, Chen KB, Chao PL: Antioxidative effect of vitamin D3 on zinc-induced oxidative stress in CNS. Ann N Y Acad Sci 2005;1053:319–329.
39. Bao B-Y, Ting H-J, Hsu J-W, Lee Y-F: Protective role of 1α, 25-dihydroxyvitamin D3 against oxidative stress in nonmalignant human prostate epithelial cells. Int J Cancer 2008;122:2699–2706.
40. Bhattacharyya A, Chattopadhyay R, Mitra S, Crowe SE: Oxidative stress: An essential factor in the pathogenesis of gastrointestinal mucosal diseases. Physiol Rev 2014;94:329–354.
41. Mokhtari Z, Hekmatdoost A, Nourian M: Antioxidant efficacy of vitamin D. J Parathyr Dis 2016;5:11–16.
42. Berridge MJ: Vitamin D cell signalling in health and disease. Biochem Biophys Res Commun 2015;460:53–71.
43. Semba RD, Moghekar AR, Hu J, *et al.*: Klotho in the cerebrospinal fluid of adults with and without Alzheimer's disease. Neurosci Lett 2014;558:37–40.
44. Di Bona D, Accardi G, Virruso C, Candore G, Caruso C: Association of Klotho polymorphisms with healthy aging: A systematic review and meta-analysis. Rejuvenation Res 2014;17:212–216.
45. Moe SM: Klotho: A master regulator of cardiovascular disease? Circulation 2012;125:2181–2183.
46. Dubal DB, Yokoyama JS, Zhu L, *et al.*: Life extension factor Klotho enhances cognition. Cell Rep 2014;7:1065–1076.
47. Wirrig EE, Gomez MV, Hinton RB, Yutzey KE: COX2 inhibition reduces aortic valve calcification in vivo significance. Arterioscler Thromb Vasc Biol 2015;35:938–947.
48. Hinz B, Brune K: Cyclooxygenase-2—10 years later. J Pharmacol Exp Ther 2002;300:367–375.
49. Hansen M, Kapahi P: 14–TOR signaling and aging. Enzym 2010;28:279–299.
50. Yin Y, Shen WH: PTEN: A new guardian of the genome. Oncogene 2008;27:5443–5453.
51. Kreis P, Leondaritis G, Lieberam I, Eickholt BJ: Subcellular targeting and dynamic regulation of PTEN: Implications for neuronal cells and neurological disorders. Front Mol Neurosci 2014;7:23.
52. Pan L, Matloob AF, Du J, *et al.*: Vitamin D stimulates apoptosis in gastric cancer cells in synergy with trichostatin A/sodium butyrate-induced and 5-aza-2′-deoxycytidine-induced PTEN upregulation. FEBS J 2010;277:989–999.
53. Zhang X, Li F, Bulloj A, *et al.*: Tumor-suppressor PTEN affects tau phosphorylation, aggregation, and binding to microtubules. FASEB J 2006;20:1272–1274.
54. Yan S Du, Bierhaus A, Nawroth PP, Stern DM: RAGE and Alzheimer's disease: A progression factor for amyloid-beta-induced cellular perturbation? J Alzheimers Dis 2009;16:833–843.
55. Chavakis T, Bierhaus A, Nawroth P: RAGE (receptor for advanced glycation end products): A central player in the inflammatory response. Microbes Infect 2004;6:1219–1225.
56. Lubitz I, Ricny J, Atrakchi-Baranes D, *et al.*: High dietary advanced glycation end products are associated with poorer spatial learning and accelerated A$β$ deposition in an Alzheimer mouse model. Aging Cell 2016;15:309–316.
57. Cai Z, Liu N, Wang C, *et al.*: Role of RAGE in Alzheimer's disease. Cell Mol Neurobiol 2016;36:483–495.
58. Tang Z, Ioja E, Bereczki E, *et al.*: mTor mediates tau localization and secretion: Implication for Alzheimer's disease. Biochim Biophys Acta Mol Cell Res 2015;1853:1646–1657.
59. Zhu S, Shala A, Bezginov A, Sljoka A, Audette G, Wilson DJ: Hyperphosphorylation of intrinsically disordered Tau protein induces an amyloidogenic shift in its conformational ensemble. PLoS One 2015;10:e0120416.
60. Braak H, Braak E, Strothjohann M: Abnormally phosphorylated tau protein related to the formation of neurofibrillary tangles and neuropil threads in the cerebral cortex of sheep and goat. Neurosci Lett 1994;171:1–4.
61. Hong Y, An Z: Hesperidin attenuates learning and memory deficits in APP/PS1 mice through activation of Akt/Nrf2 signaling and inhibition of RAGE/NF-κB signaling. Arch Pharm Res 2015. DOI:org/10.1007/s12272-015-0662-z.
62. Daborg J, von Otter M, Sjölander A, *et al.*: Association of the RAGE G82S polymorphism with Alzheimer's disease. J Neural Transm 2010;117:861–867.
63. Guo Y-X, He L-Y, Zhang M, Wang F, Liu F, Peng W-X: 1,25-Dihydroxyvitamin D3 regulates expression of LRP1 and RAGE in vitro and in vivo, enhancing Aβ1–40 brain-to-blood efflux and peripheral uptake transport. Neuroscience 2016;322:28–38.
64. Lee T-W, Kao Y-H, Lee T-I, Chang C-J, Lien G-S, Chen Y-J: Calcitriol modulates receptor for advanced glycation end products (RAGE) in diabetic hearts. Int J Cardiol 2014;173:236–241.
65. Zitman-Gal T, Golan E, Green J, Bernheim J, Benchetrit S: Vitamin D receptor activation in a diabetic-like environment: Potential role in the activity of the endothelial pro-inflammatory and thioredoxin pathways. J Steroid Biochem Mol Biol 2012;132:1–7.
66. Talmor-Barkan Y, Bernheim J, Green J, Benchetrit S, Rashid G: Calcitriol counteracts endothelial cell pro-inflammatory processes in a chronic kidney disease-like environment. J Steroid Biochem Mol Biol 2011;124:19–24.
67. Pike JW, Meyer MB: The vitamin D receptor: New paradigms for the regulation of gene expression by 1,25-dihydroxyvitamin D(3). Endocrinol Metab Clin North Am 2010;39:255–269.
68. Bouillon R, Eelen G, Verlinden L, Mathieu C, Carmeliet G, Verstuyf A: Vitamin D and cancer. J Steroid Biochem Mol Biol 2006;102:156–162.
69. Kato S: The function of vitamin D receptor in vitamin D action. J Biochem 2000;127:717–722.
70. Wang L, Hara K, Van Baaren JM, *et al.*: Vitamin D receptor and Alzheimer's disease: A genetic and functional study. Neurobiol Aging 2012;33:1844.e1–1844.e9.
71. Dursun E, Gezen-Ak D, Yilmazer S: A novel perspective for Alzheimer's disease: Vitamin D receptor suppression by amyloid-β and preventing the amyloid-β induced alterations by vitamin D in cortical neurons. J Alzheimers Dis 2011;23:207–219.
72. King L, Dear K, Harrison SL, *et al.*: Investigating the patterns and determinants of seasonal variation in vitamin D status in Australian adults: The Seasonal D Cohort Study. BMC Public Health 2016;16:892.
73. Mendez MF: Early-onset Alzheimer's disease: Nonamnestic subtypes and type 2 AD. Arch Med Res 2012;43:677–685.
74. Querfurth HW, LaFerla FM: Alzheimer's disease. N Engl J Med 2010;362:329–344.