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RESEARCH ARTICLE **OPEN ACCESS**

VITAMIN D HAS AN AETIOLOGICAL ROLE IN DEMENTIAS; MYTH OR FACT?

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ABSTRACT

Vitamin D is produced through the cutaneous transformation of 7-dehydrocholesterol by UVB-irradiation with multiple neurotrophic and neuroprotective functions, while regulating calcium-mediated neuronal excitotoxicity. Vitamin D acts mainly through binding to intracellular Vitamin D receptor (VDR) with a possible involvement of vitamin D receptor (VDR) and vitamin D-binding protein (VDBP). This is a review of evidence for the aetiological role of vitamin D in dementias and other neurological disorders. There is contradictory evidence regarding vitamin D supplementation in the prevention of dementia progression. Adding vitamin D to the standard medications used in dementia may have a future role in dementia management.

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INTRODUCTION

Vitamin D is a secosteroid hormone with a common synthetic pathway with cholesterol. It is produced endogenously through the transformation of 7-dehydrocholesterol by UVB-irradiation or obtained via absorption (Boucher, 2012). The mechanism of action of vitamin D occurs mainly through binding to intracellular vitamin D receptor (VDR), where vitamin D regulates the phenotypic stability of cell signalling components such as Ca^{2+} and reactive oxygen species (ROS) (Berridge. 2016,Tong *et al*. 2018). Vitamin D influence almost all metabolic processes such as apoptosis, inflammatory processes, differentiation and could be involved in the ageing process (Kubis and Piwowar. 2015, Anastasiou *et al*. 2014).
In the nervous system, vitamin D is involved in calcium-mediated neuronal excitotoxicity regulation, oxidative stress reduction, and neurotrophic factors induction (Mpandzou *et al*. 2016). Vitamin Dinhibits cytokines involved in T-lymphocytes differentiation and pro-inflammatory cytokine production, while regulating T-regulatory development (Speer. 2013). Vitamin D actions within the cell include control of pathways such as intracellular calcium, PKA, and PI3K signalling, improved amyloid-β (Aβ)peptides phagocytosis by macrophages and inhibited Aβ-induced apoptosis in Alzheimer's disease (Mizwicki *et al*. 2013). The world-wide incidence of vitamin D deficiency is high especially in the elderly (Alhamad *et al*. 2014). Vitamin D deficiency is common in psychogeriatric patients and in chronic diseases (Muscogiuri *et al*. 2017) and in cerebral small vessel disease (Carluccio *et al*. 2017). Alzheimer's Disease (AD) is the most common form of dementia affecting about 46 million people worldwide and is characterized by progressive loss of memory, language and cognition (Wood and Gupta. 2015). AD is characterized pathologically by extracellular amyloid plaques composed of aggregated Aβ peptides and intracellular neurofibrillary tangles containing the microtubule-associated protein tau (Grimm *et al*., 2016). AD progression is associated with oxidative/nitrosative stress, mitochondrial damage, neuroinflammation &finally neuronal cell death (Pretorius *et al*. 2016; Di Domenico *et al*. 2015). There are several risk factors related to AD as hypercholesterolemia and type 2 diabetes, but the role of pro-inflammatory cytokines and vitamin D is not fully understood (Chakrabarti *et al*. 2015).

The current pharmacological treatment for AD includes acetyl cholinesterase and/or memantine to slow the disease progression and control behavioural changes. In this review, we aim to examine the aetiology of hypovitaminosis D in dementia progression and the possible future role of vitamin Din the pharmacological management of dementia.

Vitamin D and Dementia: What is the Evidence?

Animal studies suggests that vitamin D has a role in the slowness of dementia. This was evidenced from the molecular changes after 5 months of vitamin D supplementation in transgenic AD model mice brains. These changes resulted in improved learning and memory performance (Landel *et al*. 2016). Mice fed on a diet supplemented with mushrooms - a convenient dietary source of vitamin D, displayed reduced amyloid plaque and elevated interleukin-10 (Bennett *et al*. 2013).Further animal studies suggested that vitamin D was linked to up-regulation of neurotrophic factors (Peterson *et al*. 2013). Moderate vitamin D hypovitaminosis was associated with an increase in the Aβ (Grimm *et al*. 2014). In Humans, Hypovitaminosis D could be associated with brain changes and cognitive decline (Annweiler *et al*. 2016). There is some evidence of vitamin D deficiency in Other neurological diseases such as multiple sclerosis (MS), Parkinson's disease (PD) in addition to AD (Mpandzou *et al*. 2016). Another long follow up study (6-years) confirmed the association of vitamin D deficiency and the risk of all-cause dementia (Littlejohns *et al*. 2014). In 666 non-demented participants followed for 12 years, lower vitamin D levels were associated with a higher risk of dementia (Amadieu *et al*. 2017). In a study of 498 community-dwelling women, 70 of them later developed AD (Annweiler *et al*. 2012c). The mean levels of vitamin D were significantly different for AD patients in comparison to healthy controls And mild cognitive impairment (MCI) patients (Yesil et al. 2015). Vitamin-D sufficient patients have shown a higher mini mental state examination (MMSE) scores (Oudshoorn *et al*. 2008). In another study for elderly, vitamin D deficiency was associated with declining MMSE scores (Toffanello *et al*. 2014).

In other types of dementias, vitamin D deficiency (<12 ng/ml) was associated with 2.2-fold increase in odds of vascular dementia (VaD) (Annweiler *et al*. 2011b, Prabhakar *et al*. 2015) and impairment in working memory/executive functioning (Pettersen *et al*. 2014). High dose of vitamin D supplementation could enhance performance in some aspects of Dementia such as visual memory and Paired Associates Learning Task (Pettersen. 2017) . A large US study found an association between severe vitamin D deficiency and visual memory decline but not verbal memory decline (Kuzma *et al*. 2016). In a study with more than 380 participants, rates of decline in episodic memory and executive function among vitamin D-deficient were greater (Miller *et al*. 2015). Vitamin D deficiency was shown to be associated with neuronal disruption primarily in frontal regions (Moon *et al*. 2015b). Deficits in specific cognitive domains such as executive functions, wordlist encoding, and visual memory (encoding and recall) were significantly associated with low vitamin D concentration in a study of more than 1000 individuals (Nagel *et al*. 2015). Furthermore, in 1,990 aging adults, vitamin D intake was positively associated with short-term memory improvement (Andreeva *et al*. 2014). Low vitamin D and cognitive decline was observed in multiple ethnic groups (Vedak *et al*. 2015).

Higher serum 25(OH) D concentrations showed a reduced risk of dementia in a long follow up study (17-years) of more than 5000 individuals free of dementia at baseline (Knekt *et al*. 2014). Vitamin D deficiency was also associated with lower hippocampal volumes and poorer neuropsychological function (Karakis *et al*. 2016) with higher risk of cognitive decline in the elderly with deficient vitamin D levels (Dickens *et al*. 2011). New insights in dementia pathophysiology highlighted the possible role of increased intracellular free calcium in AD nerve cells with neurofibrillar tangles with augmentation of short chain Aβ production (Fujita. 2004).Studies showed that vitamin D prevents Aβ-induced calcium elevation affecting nerve growth factor (NGF) release in cortical neurons (Gezen-Ak *et al*. 2014). Defective phagocytosis of soluble Aβ by AD macrophages could be recovered by vitamin D and is blocked by the Vitamin D Receptor; (VDR) antagonist (Mizwicki *et al*. 2012).Vitamin D supplements could enhance toll-like receptors, modulate vascular endothelial factor expression and angiogenin (Lu'o'ng and Nguyen. 2013).

Vitamin D level and the Cerebrospinal fluid (CSF) in Alzheimer's Disease: Vitamin D concentration and CSF acetyl cholinesterase (AChE) were both decreased in the CSF of AD. In AD patients, CSF AChE activity correlated positively with CSF levels of total tau ($r = 0.44$) and phosphorylated tau protein ($r = 0.50$) (Johansson *et al*. 2013). A positive correlation was found between vitamin D and cerebral blood flow in AD patients left cortex (Farid *et al*. 2012). In a study of 75 patients (29 with subjective cognitive impairment, 28 with MCI, 18 with AD), higher vitamin D levels were related to higher concentrations of CSF Aβ and bigger brain volumes (Hooshmand *et al*. 2014).

Does Vitamin D have a role in Dementia Treatment?

Vitamin D supplementation caused significant improvement in the cognitive performance in subjects with MMSE score < 24 (Gangwar *et al*. 2015) and was associated with less progression from mild AD to severe (5.4 ± 0.4 years vs. 4.4 ± 0.16 years) (Chaves *et al*. 2014). Vitamin D supplement added to memantine was found to have a neuroprotective effects in a study for 58 patients (Lemire *et al*. 2016). This was found to be related to preventing A β and glutamate neurotoxicity (Annweiler *et al*. 2014). This study was replicated confirming that adding vitamin D to memantine was superior over medications given separately. Participants on the combined treatment showed increased MMSE score by 4.0 ± 3.7 points, while taking memantine or vitamin D alone did not show an increase in MMSE (Annweiler *et al*. 2012b). A new agentdenosomin (an artificial inducer of neurite elongation) affects axonal extension via a vitamin D-membrane-associated, rapid response steroid-binding protein pathway in Aβ-damaged neurons (Sugimoto *et al*. 2015). Bexarotene, a Retinoid X receptors (RXRs) agonist used for the treatment of cutaneous T-cell lymphoma, was found to be useful in AD(Yamada and Kakuta. 2014).

Vitamin D receptor (VDR) and Vitamin D-binding protein (VDBP): Receptors for 1,25-dihydroxyvitamin D3, the metabolite of vitamin D are widely expressed in human brain. 1,25-dihydroxyvitamin D3 was found to increase 27 genes mRNA levels by at least 1.9 fold, including17 genes related to neurodegenerative and psychiatric diseases (Nissou *et al*. 2013). AD genetic mapping identified loci in chromosome 12q13 encompassing the VDR gene. VDR levels were reduced in AD hippocampal pyramidal cells (Sutherland *et al*. 1992) and VDR gene polymorphisms contributed to aging (Gussago *et al*. 2016). Two polymorphisms with linked alleles, Apa1 T and Taq1 G, were associated with risk of AD and possible interactions with other genes involved in the regulation of inflammation (Lehmann *et al*. 2011, Laczmanski *et al*. 2015). Furthermore, Single nucleotide polymorphisms (SNPs) in its 3' end was associated with PD and AD (Butler *et al*. 2011) through VDR role in reducing cerebral Aβ peptides particularly in the hippocampus (Durk *et al*. 2014). VDR SNPs in702 participants were associated with a decline in category fluency (Beydoun *et al*. 2012) by affecting vitamin D binding to its receptor resulting in neuronal damage (Gezen-Ak *et al*. 2007). VDR polymorphisms were also associated with an increase in white matter lesions (James *et al*. 2011), while VDR over expression suppressed APP transcription in neuroblastoma cells (Wang *et al*. 2012). VDR is used in a panel of 8 CSF proteins effective at identifying PD and AD (Zhang *et al*. 2008). The biologically active 1,25-dihydroxyvitamin D interacts with VDR to increase the efficiency of intestinal calcium and phosphate absorption. The final converting enzyme and VDR are found throughout the human brain, with higher intake of vitamin D associated with lower Aβ load (Mosconi *et al*. 2014). AD has been related to an increase of incompetent memory T cells and defective clearance of Aβ by macrophages (Fiala. 2010). Vitamin D binding protein (VDBP) reduced Aβ aggregation in vitro, prevented Aβ-mediated cell line death and decreased Aβ-induced synaptic loss in hippocampus (Moon *et al*. 2013). VDBP a multifunctional protein, acts as an Aβ scavenger and its serum levels were inversely related to cognitive performance (Bishnoi *et al*. 2015) and decreased in Mild cognitive impairment (Muenchhoff *et al*. 2015).

Vitamin D role in Mild Cognitive Impairment (MCI) and Neurological Disorders: Vitamin D deficiency at baseline was independently associated with the progression of MCI (Moon *et al*. 2015a). In a study with more than 1300 participants, lower vitamin D levels led to more pronounced cognitive decline (Perna *et al*. 2014) and increased serum vitamin D concentration was associated with a lower risk of MCI (Annweiler *et al*. 2012a). A potent vitamin D analogue – calcipotriol could suppress calcium-dependent α-synuclein aggregation in Parkinson's Disease (PD)(Rcom-H'cheo-Gauthier *et al*. 2017) and higher vitamin D concentrations were associated with better performance in neuropsychiatric tests (Peterson *et al*. 2013). Vitamin D deficiency is associated with a higher relapse rate, a higher number of MRI lesions and worse cognitive performance in Multiple Sclerosis (MS). In 35 adults with relapsing-remitting MS, vitamin D level was positively associated with performance on immediate and delayed recall of the Rey Complex Figure Test-nonverbal long-term memory performance but not associated with mood, intelligence, or verbal memory performance (Koven *et al*. 2013). There is evidence for vitamin D deficiency in the pathophysiology of epilepsy (Hollo *et al*. 2014) and ischemic stroke (Thouvenot and Camu. 2013).

What is the Evidence against the role of Vitamin D in Dementias?

Vitamin D deficiency has been linked with cognitive decline in several studies. But other research challenged the role of vitamin D in dementias. Most Dementia trials look specifically at the global improvement in cognition and behaviours. No associations were found between vitamin D levels and the global cognitive function in a cohort of elderly psychiatric inpatients (Lapid *et al*. 2013) and in another large cohort with 18 y follow-up, plasma vitamin D was not associated with cognitive outcomes (Olsson *et al*. 2017). Another follow-up study showed no correlation between 25(OH) D and depression/or dementia (Cartier *et al*. 2017). Studies of visuoconstructional abilities, visual memory and processing speed did not support a role of vitamin D level (Overman *et al*. 2016) Serum 25(OH) D status was not significantly associated with neuroimaging abnormalities (Littlejohns *et al*. 2016) and there were no significant association between lower levels of vitamin D with lower cognitive scores at baseline, change in scores over time or dementia risk(Schneider *et al*. 2014). No association between vitamin D and plasma Aβ levels in 1,219 cognitively healthy elderly was found (Gu *et al*. 2012). Furthermore, there are concerns about the lack of consensus regarding the level of vitamin D regarded as deficiency.

DISCUSSION

Ageing is considered the most significant risk factor for Dementia.AD is characterized by an activation of the cerebral immune system, glutamatergic excitotoxicity that results in neuronal death and a decrease in brain cholinergic activity. The currently available medications; acetyl cholinesterase inhibitors and memantine are used for symptomatic treatment, slowness of AD progression and controlling behavioural changes (Annweiler and Beauchet. 2012). Dietary products rich in vitamins such as fruits, vegetables, grains and fish were suggested to be protective against AD, where diet increasing the risk include meat, and high-fat dairy products (Grant. 2016). Vitamin D represents a promising therapeutic tool for reducing cytokine-mediated neuroinflammation in AD (Magrone *et al*. 2012), The deficiency of vitamin D is a worldwide significant problem with an estimates 1 billion affected (Iwamoto *et al*. 2012).The older population are at particularly risk due to decreased cutaneous synthesis &dietary intake (Schlogl and Holick. 2014) . It was shown that 2/3 of over 65 years have insufficient serum vitamin D (Ribera Casado. 2012). Vitamin D deficient individuals, especially elderly could be candidates for vitamin D supplementation (Keeney and Butterfield. 2015). Cognitive impairment in older people is an established risk factor for falls and AD individuals are at higher risk for fractures (Casas Herrero *et al*. 2011). The role of vitamin D could provide added protection infractures and dementia at the same time (Hanyu. 2015).

Hypovitaminosis D (< or =20 ng/mL) was associated with more than twice the odds of all-cause dementias (odds ratio [OR] = 2.3) and in particular AD (OR = 2.5) (Buell *et al*. 2010) and also associated with brain structural abnormalities (Berridge. 2015) and cerebrovascular events such as large vessel infarcts and fatal stroke (Soni *et al*. 2012). Experts believe that hypovitaminosis D increases the risk of cognitive decline (Annweiler *et al*. 2016, Manzo *et al*. 2016). Animal studies show that vitamin D supplementation is protective and enhances learning and memory performance (Annweiler. 2016). Further research supported these opinions (van der Schaft *et al*. 2013); however, these studies were mostly observational (Sommer *et al*. 2017), and other studies failed to associate increased vitamin D levels with improved cognitive outcomes (Landel *et al*. 2016a). There are several proteins at the molecular level linking AD to vitamin D levels such as VDR, apolipoprotein E, L-type voltage-sensitive calcium channels, nerve growth factor and nitric oxide synthase (Lu'o'ng and Nguyen. 2013). Future combination of drugs therapies such as memantine with vitamin D could be considered in the management of Dementia and other neurodegenerative diseases (Annweiler *et al*. 2011a). Vitamin D combined with resveratrol (Nutritional compound with neuroprotective effects) showed a reduction in soluble Aβ and phosphorylation of tau in mice hippocampus (Cheng *et al*. 2017). It appears there is evidence for vitamin D supplement on several domains in dementia, but the global clinical improvement is still not fully understood. Further studies, randomized trials and medications licensing approvals are needed to reveal the full clinical benefit of vitamin D as a treatment or an augmentation in neurological conditions including dementias (Balion *et al*. 2012).

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