

The Correlation between Vitamin D and Cognition: A Review

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ABSTRACT

Background: During the last 25 years, vitamin D -being a member of the superfamily of nuclear steroid transcription regulators - has emerged as a serious candidate in nervous system development and function and a therapeutic tool in a number of neurological pathologies. More recently, experimental and pre-clinical data suggest a link between vitamin D status and cognitive function. Human studies strongly support a correlation between low levels of circulating 25-hydroxyvitamin D (25(OH)D) and cognitive impairment or dementia in aging populations. In parallel, animal studies show that supplementation with vitamin D is protective against biological processes associated with Alzheimer's disease (AD) and enhances learning and memory performance in various animal models of aging and AD. More recently epidemiological associations have been made between low vitamin D and psychiatric disorders not typically associated with abnormalities in brain development such as depression and Alzheimer's disease

Aim of the Study: was to review the recent literature to investigate the correlation between vitamin D status and neurocognitive function.

Methods: We searched the medical literature to retrieve studies for the review to 30 November 2017. electronic search in the scientific database from 1965 to 2017– (Medline, Embase, AMED, Psych INFO, the Cochrane Library websites were searched for English Publications were obtained from both reprint requests and by searching the database. Data extracted included authors, country, year of publication, characteristics of patients, pathophysiology, risk factors, clinical manifestations, different diagnostic approaches and treatment modalities.

Conclusion: Accumulating evidence in the current literature indicate that vitamin D deficiency is highly prevalent among patients with cognitive impairment, and that low vitamin D status may negatively impact cognition and that hypovitaminosis D is usually associated with increased risk of developing AD and dementia. Nevertheless, while vitamin D supplementation is safe for those with cognitive impairment, there is no solid proof that they will see significant improvement in their symptoms.

Keywords: cognitive function, vitamin D, Dementia, Alzheimer's disease, Hypovitaminosis D, VDR, 25-hydroxyvitamin D (25(OH)D).

INTRODUCTION

Hypovitaminosis D- in other words Vitamin D deficiency- lessens vitamin D activity in a variety of organs, including the central nervous system. Low 25-hydroxyvitamin D [25(OH)D] levels are prevalent in older individuals, and adults with cognitive difficulties have been shown to have hypovitaminosis D^[1]. There is a biologically plausible link between vitamin D and cognitive function. The vitamin D receptor (VDR), vitamin D metabolites and enzymes required for vitamin D activation have been found in the brain and central nervous system. Additionally, experimental studies have demonstrated that active vitamin D may influence brain and neuron development, and have

neuroprotective potential and antioxidant effects^[2]. Studies on VDR knockout mice have demonstrated that hypovitaminosis D may play a role in accelerated ageing, behavioural, social, motor and sensory deficits^[3]; all of which can contribute to cognitive decline.

The consolidation of information in the brain is the basis for learning and memory. Various threads of information can be stored in many parts of the brain, such as the cortex and the hippocampus. The hippocampus, which is located in the middle temporal lobe, plays an important role in mammalian spatial learning and memory consolidation^[4]. Low levels of vitamin D in elderly people are associated with age-related disorders, including cancer, metabolic disorders, and vascular diseases^[5].

Learning and memory cause long-term changes in nerve cell activity.

Thus, when certain synapses in large quantities are used, the efficiency of these synapses improves in the long term^[6].

N-methyl-D-aspartate receptor activity is required to strengthen the inward flow of calcium ion. Any imbalance in the amount of free calcium ions is associated with impairment in learning. Several studies on the nervous system have suggested that vitamin D can determine cognitive phenomena by acting on intracellular calcium homeostasis through different ways^[7].

Vitamin D deficiency impairs the spatial learning process and, during pregnancy, may diminish the formation of long-term potentiation^[8]. Notwithstanding the vitamin D benefits confirmed in previous works, other studies have indicated that vitamin D deficiency is not involved in the completion of cognitive tasks and the functioning of spatial and working memory^[9]. Structural integrity and neuronal functions are critical in learning and memory processes, and vitamin D has been shown to contribute to the maintenance of healthy neurons. Vitamin D protects cortical cells against damage to neurons through increased messenger RNA expression^[10]. A number of mechanisms that determine the relationship between low levels of vitamin D and the risk of dementia have been identified, even though although the biological mechanisms of this association are insufficiently clear, low levels of vitamin D are associated with increased white matter^[11].

Considering these findings, in 2014 a group of international experts came to the consensus that hypovitaminosis D should be considered a risk factor for cognitive decline and dementia as it may change the clinical presentation of dementia due to accompanying comorbidities, but that 25(OH)D should not be used as a diagnostic or prognostic biomarker. The authors concluded that vitamin D supplementation should be part of the care management of older adults with cognitive disorders^[12]. However, whether vitamin D plays a causal role in cognitive decline directly or through its impact on comorbidities, or whether it is a consequence of cognitive decline remains unclear.

The aim of the present study was to ascertain the relationship between vitamin D and cognition.

MATERIALS AND METHODS

Electronic search in the scientific database from 1960 to November 2017.

Data Sources: Literature searches of Medline, Embase, AMED, Psych INFO, the Cochrane Library websites between January 1960 until November 2017 were performed. The search terms were used in combinations and together with the Boolean operators OR and AND; Search terms used were: (“vitamin D” or “vitamin D2” or “vitamin D3” or “25OHD” or “25(OH)D” or “25-hydroxyvitamin D” or “Hydroxycholecalciferols” or “hypovitaminosis D”) and 10 for cognition (“cognition” or “cognitive” or “memory” or “attention” or “executive functions” or “dementia” or “mild cognitive impairment” or “mini mental state examination” or “MMSE” or “neuropsychological”). Citations from previous published literature were also searched.

Data extracted included authors, country, year of publication, age and sex of patients, epidemiology, geographical distribution, pathophysiology, risk factors, clinical manifestations, and investigations.

The study was done after approval of ethical board of King Abdulaziz university.

VITAMIN D: SOURCE, MODE OF ACTION AND BIOLOGICAL FUNCTION

The term vitamin D also represents D2, D3 or both (D2 is less active than D3). It is produced in the skin from sun exposure or obtained from foods that naturally contain vitamin D including cod liver oil, fatty fish (salmon, mackerel, sardines and tuna), foods fortified with D (milk and some cereals) and supplement pills. When the skin is exposed to sunlight, 7dehydrocholesterol (in all layers of the skin) is converted to Pre-vitamin D3. 95% of pre-vitamin D3 is in the epidermis and cannot be removed by skin washing. Pre-vitamin D3 is converted to D3 and some is converted by photo-conversion to other products like 7dehydroxy cholesterol and lumisterol. These latter two products are inactive on calcium metabolism and are produced during prolonged exposure to ultraviolet B radiation from the sun, preventing sun induced vitamin D intoxication^[13].

Cutaneous vitamin D3 is influenced by skin pigmentation, sunscreen use, time of day, season, latitude, altitude and air pollution. In winter, early morning and late afternoon, the solar UV-B photons have to travel through the ozone layer, which absorbs these rays. In places where sun shines 24 hours a day (e.g. far northern and southern regions of the world in summer), vitamin D synthesis occurs only between 10 a.m. to 3 p.m. because of this ozone phenomenon. In cities like Los Angeles and Mexico City where there are high nitrous oxide and ozone

levels, little UV-B photons reach people. Glass also absorbs all UV-B radiation and no D3 is produced [14].

When vitamin D3 is formed, it travels to dermal capillaries by vitamin D binding protein (DBP). Ingested vitamin D is incorporated into chylomicrons that enter the lymphatic system, venous blood and binds to DPB. DPB and vitamin D3 are transported by the blood to the liver. D2 and D3 produced in this fashion are 25-hydroxylated by the liver to the major circulating vitamin D metabolite, vitamin D 25 Hydroxylase (25(OH)D). This metabolite 25(OH)D is what is measured when we order a blood test. 25(OH)D is hydroxylated in the kidney to form 1,25(OH)2D [13]. This product does the following: Regulates gene transcription through a vitamin D receptor (VDR). It binds to specific nucleotide sequences in DNA. This allows regulation of 200-2000 genes. Vitamin D levels will affect the expression of genes that have a variety of biological functions linked to calcium, autoimmune disorders and cardiovascular diseases. VDR is present in most tissues and cells in the body including brain, vascular smooth muscle, prostate, breast, and macrophages [14].

Properties and source of Vitamin D

By definition, Vitamin D is a multipurpose, fat-soluble, seco-steroid hormone. The two most important forms of vitamin D are cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). D3 is produced in the skin by sunlight, while the latter is contained in some fruits and vegetables and fortified foods. These forms of vitamin D are inactive until they are metabolized by the liver and kidney [15]. Once biologically active, vitamin D binds to

intracellular VDRs, such as those expressed on neurons [15,16]. It is the interaction with these VDRs that enables vitamin D to act on a cellular level. Serum 25(OH)D is the active metabolite of cholecalciferol and ergocalciferol that is usually measured to determine the Vitamin D status of an individual [16].

Vitamin D acquisition, metabolism and modes of action.

Cholecalciferol or vitamin D3 and ergocalciferol or vitamin D2 follow the same metabolic pathway. Blood metabolites include 25(OH)D produced by the liver, which is bound to vitamin D binding protein. Renal and extra-renal CYP27B1 (1 α -hydroxylase) produces the active metabolite 1,25(OH)2D. 25(OH)D or 1,25(OH)2D, which enters the cell through passive diffusion or megalin-dependent transport. Once inside the cell, 1,25(OH)2D binds to its nuclear receptor VDR and after dimerization with retinoid X receptor (RXR), forms a regulatory complex which can bind target genes that contain a vitamin D responsive element (VDRE). 1,25(OH)2D can also induce rapid non-genomic responses by binding to its membrane receptor MARRS or a membrane VDR and regulate the activity of adenylate cyclase, PLC and PKC proteins. 1,25(OH)2D also induces modulation of calcium release from intracellular stores and can interact with TGF and EGF receptors to modulate cell cycle processes. These different modes of action and the cross talks operated by vitamin D signaling ultimately lead to transcription modulation of hundreds of genes, depending on the cell-type considered [17].

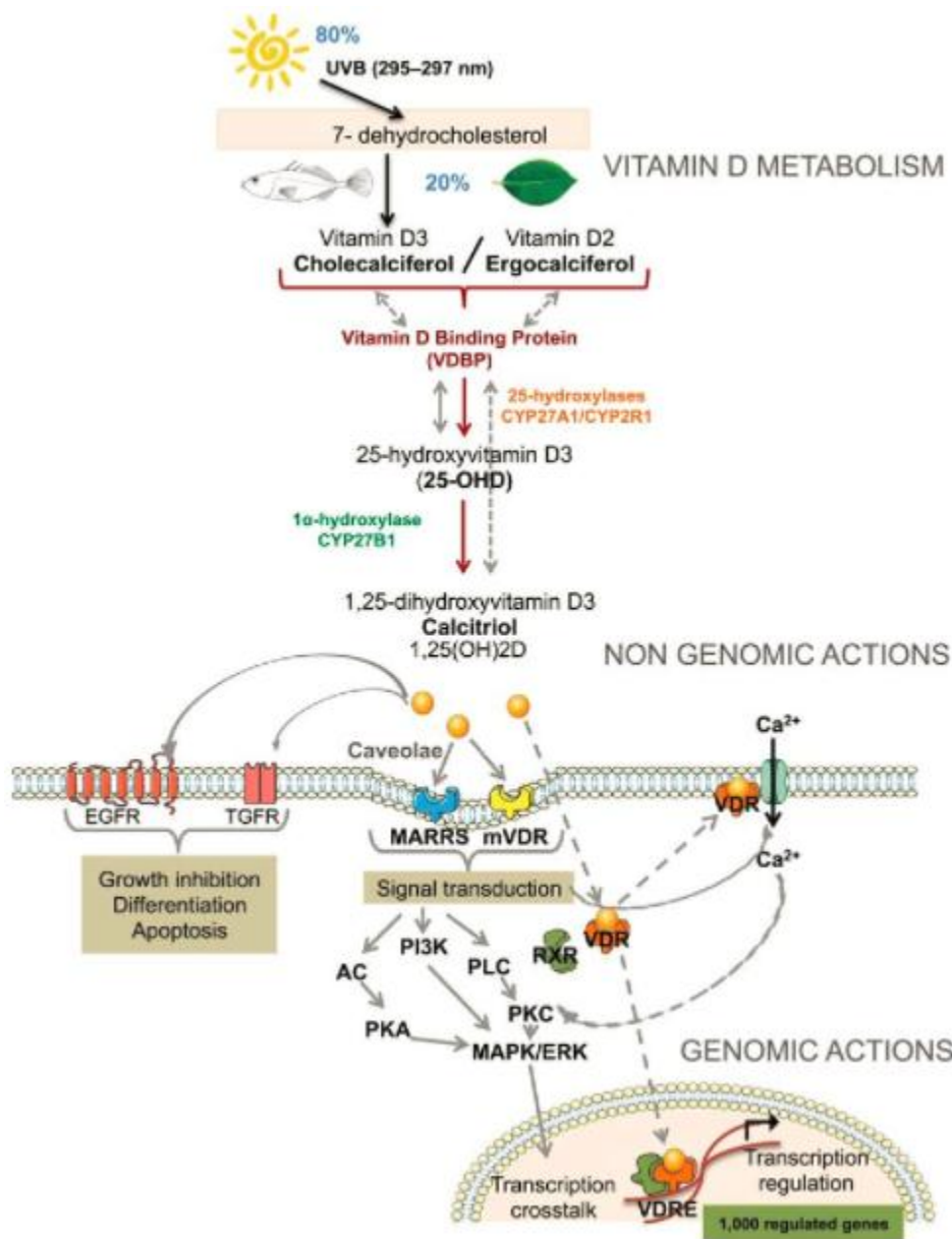


Figure 1: Vitamin D mode of action ^[17].

Hypovitaminosis D prevalence

Vitamin D Deficiency; also called hypovitaminosis D, is prevalent among older adults due to both low dietary intake and inadequate sun exposure ^[18]. Almost 50-80% of elderly people have low vitamin D levels. Nevertheless, due to lack of screening, the proportion of the geriatric population that has unrecognized vitamin D deficiency may be much larger. Those at highest risk for low vitamin D status include individuals with low sunlight exposure, females, those with poor nutrition, people who have dark pigmented skin, and the elderly ^[19]. There is some discrepancy about how much of the vitamin is

enough. Vitamin D deficiency is defined by some as a 25(OH)D value less than 20 ng/mL. Some researchers further separate the categories into insufficiency (values less than 10 ng/mL), deficiency (values from 10-20 mL), and sufficiency (values greater than 20 ng/mL), yet, others use a less lenient value to define deficiency (any value less than 25 ng/mL) ^[20].

It has been estimated that 1 billion people worldwide suffer vitamin D deficiency or insufficiency, although this prevalence is still uncertain and difficult to account for ^[21]. According to a recent systematic review, this global public health issue varies strongly depending on geographical

location, age, and gender, and it appears that all subgroups of population are at risk for vitamin D deficiency [22]. Another systematic review of 195 vitamin D studies involving more than 168,000 individuals from 44 countries reported that 37% of the participants had 25(OH)D seric concentrations below 20ng/mL (50nmol/L), and only 11.9% were above 30ng/mL (75nmol/L) [23]. Within these 1 billion people affected by vitamin D insufficiency, elderly people seem particularly at risk, especially when institutionalized or in hospitals. For instance, in Europe and the USA, at latitudes higher than 40°, between 40% and 90% of elderly people, depending on the definition of deficiency considered, suffer from hypovitaminosis D [24]. This high prevalence in the elderly community can be explained by several factors: decreased sun exposure and diminished levels of 7-dehydrocholesterol within the epidermis leading to reduced dermal production of vitamin D, poorer dairy and vitamin D intake, alteration of vitamin D metabolism due to renal or hepatic failure, and increased catabolism due to medication (immunosuppressors, glucocorticoids, antiepileptics) [25]. A deficiency in vitamin D has been linked to many human diseases, particularly those that are age-related, such as Alzheimer's disease (AD), cancer, cardiovascular disease, type II diabetes, multiple sclerosis, and various inflammatory disorders. Hypovitaminosis D is therefore not to be undermined, not only for optimal bone health, but also in regards of all-cause mortality, as pointed out by a recent systematic review by Rush L *et al.* [26].

VITAMIN D AND COGNITIVE IMPAIRMENT

There is an abundance of research showcasing the role of vitamin D deficiency in cognitive impairment risk. Here are only a handful of the studies connecting vitamin D status to cognition:

- According to a 2017 systematic review and meta-analysis of 26 observational and 3 intervention studies including over 19,000 participants, low vitamin D status was associated with cognitive decline (odds ratios (OR): 1.26) and poorer cognitive performance (OR: 1.24) among participants without dementia. However, this study did not find a significant benefit of vitamin D supplementation on cognition [27].
- A study published in 2017 evaluated the role of vitamin D status in cognition among 369 individuals. The researchers found that those who were vitamin D deficient experienced a faster rate of cognitive decline. Additionally,

vitamin D deficiency was associated with a nearly 3-fold increased risk of developing Alzheimer's disease with a hazard ratio of 2.85 [28].

- A 2016 study found that vitamin D deficiency increased elderly Chinese individual's risk of developing dementia by over twofold. In addition, dementia risk increased as vitamin D levels decreased [29].
- Research published in 2015 found that severe vitamin D deficiency was independently associated with future risk of mild cognitive impairment and dementia among elderly individuals. This was especially significant in those whose baseline cognitive function had decreased only modestly, researchers also discovered that vitamin D status is linked to poorer neurological skills Schoolbut not dementia or Alzheimer's disease [30].
- A study published in the *Canadian Journal of Neurological Sciences* found that both vitamin D insufficiency and seasonal decline of vitamin D levels are correlated with lower scores related to cognitive performance [31].
- A meta-analysis and review reported that lower vitamin D levels are associated with decreased cognitive function and an increased risk of Alzheimer's disease [32].
- A 2015 study suggested cognitive ability of individuals with low 25(OH)D declined three times faster than that of healthy subjects with 25(OH)D above 20 ng/ml [33].

Consequences of vitamin D deprivation on brain structures

Few studies have investigated the effect of inadequate vitamin D status on brain structures. In terms of brain volumetry, it was shown that rats born to vitamin D-deficient mothers had profound alterations in the brain at birth compared to control animals, with a thinner cortex and enlargement of the lateral ventricles [34]. In humans, no significant difference in whole-brain volume and sulcal grade according to serum vitamin D levels was observed in one study [35], whereas in another one, an association between vitamin D concentration and ventricular volume (a proxy for brain atrophy) was found in older adults [35]. This difference only applied to the main ventricular bodies, and not to the temporal horns. Consistently, no difference in hippocampal volume was reported according to vitamin D levels amongst older community dwellers in the former study [35]. Studies in rats to examine brain vascular

changes showed that vitamin D attenuated cortical infarction induced by cerebral arterial ligation. In humans, a meta-analysis showed clearly, in both cross-sectional and longitudinal studies, that the risk of stroke was increased with hypovitaminosis D^[36]. Of interest, this finding was also true for more subtle changes such as white matter damage^[35], which is thought to disrupt cortical–subcortical white matter tracts that connect important cognitive regions of the brain^[37]. Thus, it is possible that cerebrovascular changes linked to hypovitaminosis D could explain some higher-level disorders in older adults.

VITAMIN D AND ALZHEIMER'S DISEASE

A major public health problem is the progression of dementia and noncommunicable diseases such as AD. AD is a neurodegenerative condition characterized clinically by progressive cognitive decline and, histologically, by senile plaques and neurofibrillary tangles. The major component of senile plaques is the amyloid- β protein (A β), which is produced by the sequential proteolysis of a ubiquitous transmembrane protein, amyloid- β protein precursor (A β PP). Accumulation of A β , accompanied by increased inflammatory responses in the brain, is now viewed as a direct cause of neurodegeneration and cognitive decline. It is estimated that over 25 million people worldwide suffer from dementia, with a predicted 5 million new cases per year^[38].

The etiology of the disease is still not fully understood. The first paper suggesting a link between vitamin D and AD dates back to 1992 when Sutherland and colleagues reported decreased VDR mRNA levels in the hippocampus of AD patients^[39]. It is now relatively well established that patients with AD present lower concentrations of circulating 25(OH)D when compared to matched controls. Moreover, a consequential number of genetic studies have identified polymorphisms in the VDR or megalin genes that are associated to increased risks of cognitive decline or AD. The first study suggesting a possible genetic association between the VDR and AD dates back to 2007, where the authors indicate that a polymorphism in the VDR region increases the risk of AD by 2.3 times.

Additionally, it appears that single nucleotide polymorphisms (SNPs) in the VDR gene might be a cause for some of the alterations in the vitamin D-VDR pathway^[40]. Genotyping of 563 participants over 85 years old for 5 different polymorphisms in the VDR gene revealed an association between gene variance and age-related changes in cognitive

functioning. More specifically, carriers of *BamI* and *TaqI* polymorphisms presented with worse cognitive functioning unlike carrier of the *Apal* variant^[41]. Moreover, the frequency of VDR polymorphisms *TaqI*, *Apal*, *FokI* and *BsmI* were investigated in 108 AD patients versus 77 healthy controls of the Lower Silesian population cohort. The study did not reveal any significant difference between the two groups for frequency of the *TaqI*, *FokI* or *BsmI* polymorphisms.

However, the frequency for allele A of *Apal* was higher in the control group, which was later associated with a 30% lower risk of AD in Polish and British populations study.

The authors note an important difference of risk alleles for these VDR polymorphisms depending on the population studied, suggesting a dependency on ethnic origin and climatic conditions. Another study by Wang and colleagues demonstrated a strong association between a SNP within the transcription factor Cdx-2 binding site and late-onset AD (492 AD cases versus 496 controls). The authors show that the risk allele for CDX2 is associated with lower VDR promoter activity^[42].

It was found that the frequency of “TaubF” haplotype (alleles of *TaqI*, *Apal*, *Tru9I*, *BsmI* and *FokI*, respectively) was significantly higher in the patient group with AD compared to the controls and can be considered a risk factor for the disease^[40]. Finally, sex-specific gene variations in the VDR and megalin genes have been shown to modify age-related cognitive decline in a cohort of US adults aged 50 years and older^[42].

LOW VITAMIN D AND DEMENTIA

Dementia is defined as cognitive decline resulting in memory deterioration and impaired daily functioning, and its development may involve several mechanisms. Signs and symptoms of decreased cognition in persons of advanced age are connected to both biological and environmental factors. By determining the role that vitamin D plays in these mechanisms, researchers have the capacity to improve overall health and decrease morbidity in the aging population^[43].

Only a few articles have studied this topic. Annweiler *et al.*^[44] followed 498 community dwelling woman free of Vitamin D supplements, in an epidemiology study on osteoporosis in France. Instead of measuring vitamin D levels in the blood they evaluated dietary intake of all sources of vitamin D. This study relied on participants filling

out a detailed survey sheet. Numerous cofounders were incorporated from age, BMI, sun exposure, depression and seasonal variation. In a seven-year study, 70 women developed Alzheimer's disease. They had lower vitamin D intake than the 361 non-demented participants. Of interest is that the group that developed other dementias other than Alzheimer's had normal vitamin D intake. The main limitations of this information is that estimation of total vitamin D intake is just an estimation and depends on filling out a survey sheet, certainly not as accurate as measuring vitamin D blood levels. The other dementia cases did not include vascular dementia, which has been shown to correlate directly with vitamin D levels. The other dementia cases in their study were related to neurosurgical or metabolic mechanisms, which have no known relationship to vitamin D status.

In a study previously mentioned ^[45], Buell, et al. studied 318 participants who had vitamin D levels, MRI measures of cerebral vascular disease and who developed dementia during a four-year study.

25(OH) D levels were deficient (<10 ng/ml) in 14.5 %, and insufficient (< 10-20 ng/ml) in 44 % of participants. Twenty three % developed dementia, one half were probable Alzheimer's disease. There was a much higher prevalence of dementia among those with 25(OH) D insufficiency (<20 ng/ml); 30 % vs 14 %. These vitamin D deficiency levels were associated with increased white matter hyperintensity and prevalence of white matter infarcts (10 % vs 7 %). Overall, taking all the cofounders into the study, vitamin D deficiency/insufficiency was associated with greater than twice the odds of all causes of dementia, Alzheimer's and stroke (on MRI) (with or without dementia symptoms). This study suggested a vascular protected role of vitamin D as suggested by the meta-analysis study ^[46].

It is important to remember that vitamin D appears to have other important roles evident in animal studies; reduces hippocampal degenerative processes; involved in detoxification by interacting with reactive oxygen and nitrogen species; improves neuronal survival by vitamin D related intraneuronal calcium homeostasis; may ameliorate the adverse effects of the amyloid hypothesis of Alzheimer's disease because it may attenuate AB42 accumulation by stimulating the immune system, specifically the phagocytosis and clearance of amyloid Beta protein.

Also, rodent studies, have shown an increase in choline acetyltransferase activity (this increases

acetylcholine availability) in several brain regions involved in memory ^[44].

CONCLUSION

Accumulating evidence designate that Vitamin D as a neurosteroid could be important in aging and age-related cognitive decline. Furthermore, numerous preclinical and clinical studies suggest that hypovitaminosis D may be associated with increased risk of developing AD and dementia.

Nevertheless, future randomized trials should take into account the D-tails of every individual included in the cohorts.

REFERENCES

1. **Etgen T, Sander D, Bickel H, Sander K and Förstl H(2012):** Vitamin D deficiency, cognitive impairment and dementia: a systematic review and meta-analysis. *Dementia and geriatric cognitive disorders*, 33: 297–305 .
2. **Garcion E, Wion-Barbot N, Montero-Menei C, Berger F, Wion D(2002):** New clues about vitamin D functions in the nervous system. *Trends in Endocrinology & Metabolism*, 13:100–105 .
3. **Keisala T(2009):** Premature aging in vitamin D receptor mutant mice. *The Journal of steroid biochemistry and molecular biology*,115: 91–97 .
4. **Squire LR(1992):** Memory and the hippocampus-A synthesis from findings with rats, monkeys, and humans. *Psychol Rev.*,99: 195-231.
5. **Bouillon R, Carmeliet G, Lieben L, Watanabe M, Perino A, Auwerx J, Schoonjans K, Verstuyf A(2014):** Vitamin D and energy homeostasis: Of mice and men. *Nat Rev Endocrinol.*, 10: 79-87.
6. **Bliss TV, Collingridge GL(1993):** A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*, 361: 31-39.
7. **Hu R, Zhao SG, Wang DS, Wen SR, Niu GM, A R, Wang Z, Jiang MF, Zhang CY(2012):** A prevalence study on mild cognitive impairment among the elderly populations of Mongolian and Han nationalities in a pastoral area of Inner Mongolia. *Zhonghua Liu Xing Bing Xue Za Zhi.*,33: 364-367.
8. **Grecksch G, Rüttrich H, Höllt V, Becker A(2009):** Transient prenatal vitamin D deficiency is associated with changes of synaptic plasticity in the dentate gyrus in adult rats. *Psychoneuroendocrinol.*,34: 258-264.
9. **Burne TH, McGrath JJ, Eyles DW, Mackay-Sim A(2005):** Behavioural characterization of Vitamin D receptor knockout mice. *Behav Brain Res.*,157: 299-308.
10. **Taniura H, Ito M, Sanada N, Kuramoto N, Ohno Y, Nakamichi N, Yoneda Y(2006):** Chronic vitamin D3 treatment protects against neurotoxicity by glutamate in association with upregulation of vitamin

- D receptor mRNA expression in cultured rat cortical neurons. *J Neurosci Res.*,83: 1179-1189.
11. **Hooshmand B, Lokk J, Solomon A, Mangialasche F, Miralbell J, Spulber G, Annerbo S, Andreasen N, Winblad B, Cedazo-Minguez A, Wahlund LO, Kivipelto M(2014):** Vitamin D in relation to cognitive impairment, cerebrospinal fluid biomarkers, and brain volumes. *J Gerontol A Biol Sci Med Sci .*, 69: 1132-1138.
 12. **Annweiler C(2015):** Vitamin D and cognition in older adults': updated international recommendations. *Journal of internal medicine* ,277:45–57 .
 13. **Devere R(2014):** Cognitive Consequences of Vitamin D Deficiency. *Practical Neurology*, 13(1):25-8.
 14. **Hossein-Nezhad A, Holick M(2013):** Vitamin D for Health: A Global Perspective. *Mayo Clinic Proceedings* , 88(7): 720-755
 15. **Hayes DP(2010):** Vitamin D and ageing. *Biogerontology*,11(1):1-16.
 16. **Oudshoorn C, Mattace-Raso F, van der Velde N, Colin EM, van der Cammen T(2008):** Higher serum vitamin D3 levels are associated with better cognitive test performance in patients with Alzheimer disease. *Dement Geriatr Cogn Disord.*, 25:539-540.
 17. **Landel V, Annweiler C, Millet P, Morello M, Féron F(2016):** Vitamin d, cognition and alzheimer's disease: the therapeutic benefit is in the d-tails. *Journal of Alzheimer's Disease*, 53(2):419-44.
 18. **Cherniak EP, Florez H, Roos BA, Troen BR, Levis S(2008):** Hypovitaminosis D in the elderly: from bone to brain. *J Nutr Health Aging*,12(6):366-373.
 19. **Johnson MA, Fischer JG, Hawthorne NA, Gunter EW(2003):** Vitamin D insufficiency in the Georgia Older Americans Nutrition Program. *Faseb Journal*,17(4):A691-A691.
 20. **Luckhaus C, Mahabadi B, Grass-Kapanke B et al.(2009):** Blood biomarkers of osteoporosis in mild cognitive impairment and Alzheimer's disease. *J Neural Transm .*,116:905-906.
 21. **Holick MF ((2007) :** Vitamin D deficiency. *N Engl J Med* .,357: 266–281.
 22. **Palacios C and Lilliana G ((2014):** Is vitamin D deficiency a major global public health problem? *J Steroid Biochem Mol Biol.*, 144: 138–145.
 23. **Hilger J , Friedel A , Herr R , Rausch T , Roos F , Wahl DA , Pierroz DD , Weber P , Hoffmann K ((2014):** A systematic review of vitamin D status in populations worldwide. *Br J Nutr.*, 111: 23–45.
 24. **Fardellone P , Seberty JL , Garabedian M , Bellony R , Maamer M , Agbomson F , Brazier M (1995) :** Prevalence and biological consequences of vitamin D deficiency in elderly institutionalized subjects. *Rev Rhum Engl Ed.*, 62: 576–581
 25. **MacLaughlin J , Holick MF (1985):** Aging decreases the capacity of human skin to produce vitamin D3. *J Clin Invest.*, 76: 1536–1538.
 26. **Rush L , McCartney G , Walsh D , MacKay D (2013) :** Vitamin D and subsequent all-age and premature mortality: A systematic review. *BMC Public Health*, 13: 679.
 27. **Goodwill AM, Szoek C(2017):** A Systematic Review and Meta-Analysis of The Effect of Low Vitamin D on Cognition. *Journal of the American Geriatrics Society*, DOI: 10.1111/jgs.15012
 28. **Feart C(2017):** Associations of lower vitamin D concentrations with cognitive decline and long-term risk of dementia and Alzheimer's disease in older adults. *Alzheimer's & Dementia*, 27:34-38.
 29. **Matchar DB, Chei CL, Yin ZX, Koh V, Chakraborty B, Shi XM, Zeng Y(2016):** Vitamin D Levels and the Risk of Cognitive Decline in Chinese Elderly People: the Chinese Longitudinal Healthy Longevity Survey. *The Gerontological Society of America*, 20:1-16.
 30. **Karakis I(2015):** Association of Serum Vitamin D with the Risk of Incident Dementia and Subclinical Indices of Brain Aging: The Framingham Heart Study. *Journal of Alzheimer's Disease*, 20:11-16.
 31. **Pettersen J(2014):** The Effects of Vitamin D Insufficiency and Seasonal Decrease on Cognition. *The Canadian Journal of Neurological Sciences*, 25:22-26.
 32. **Balioni C, Griffith LE, Stifler L et al(2012):** Vitamin D, cognition, and dementia: A systematic review and meta-analysis. *Neurology*,44:35-38.
 33. **Miller JW, Harvey DJ, Beckett LA, Green R, Farias ST, Reed BR, Olichney JM, Mungas DM, DeCarli C(2015):** Vitamin D Status and Rates of Cognitive Decline in a Multiethnic Cohort of Older Adults. *JAMA Neurol.*,33:45-48.
 34. **Eyles D, Brown J, Mackay-Sim A, McGrath J, Feron F(2003):** Vitamin D3 and brain development. *Neuroscience* , 118: 641–53.
 35. **Buell JS, Dawson-Hughes B, Scott TM et al.(2010):** 25-Hydroxyvitamin D, dementia, and cerebrovascular pathology in elders receiving home services. *Neurology*,74: 18–26.
 36. **Brøndum-Jacobsen P, Nordestgaard BG, Schnohr P, Benn M(2013):** 25-hydroxyvitamin D and symptomatic ischemic stroke: an original study and meta-analysis. *Ann Neurol .*, 73: 38–47.
 37. **Annweiler C, Montero-Odasso M(2012):** Vascular burden as a substrate for higher-level gait disorders in older adults. A review of brain mapping literature. *Panminerva Med.*,54: 189–204.
 38. **Prince M , Bryce R , Albanese E , Wimo A , Ribeiro W , Ferri CP (2013) :** The global prevalence of dementia: A systematic review and metaanalysis. *Alzheimers Dement.*, 9: 62–75.
 39. **Sutherland MK , Somerville MJ , Yoong LK , Bergeron C , Haussler MR , McLachlan DR (1992):** Reduction of vitamin D hormone receptor mRNA levels in Alzheimer as compared to Huntington

hippocampus: Correlation with calbindin-28k mRNA levels. *Brain Res Mol Brain Res.*, 13: 239–250.

- 40. Gezen-Ak D , Dursun E , Bilgic B , Hanagasi H , Ertan T , Gurvit H , Emre M , Eker E , Ulutin T , Uysal O , Yilmazer S (2012):** Vitamin D receptor gene haplotype is associated with late-onset Alzheimer's disease. *Tohoku J Exp Med.*, 228: 189–196.
- 41. Laczmanski L , Jakubik M , Bednarek-Tupikowska G , Rymaszewska J , Sloka N , Lwow F (2015) :** Vitamin D receptor gene polymorphisms in Alzheimer's disease patients. *Exp Gerontol.*, 69: 142–147.
- 42. Wang L , Hara K , Van Baaren JM , Price JC , Beecham GW , Gallins PJ , Whitehead PL , Wang G , Lu C , Slifer MA , Zuchner S , Martin ER , Mash D , Haines JL , Pericak-Vance MA , Gilbert JR (2012):** Vitamin D receptor and Alzheimer's disease: A genetic and functional study. *Neurobiol Aging*, 33: ,1844 -1841.
- 43. Devere R(2014):** Cognitive Consequences of Vitamin D Deficiency. *Practical Neurology*, 13(1):25-8.
- 44. Annweiler C, Beauchet O(2011):** Vitamin D-mentia: randomized clinical trials should be the next step. *Neuroepidemiology* , 37: 249-258.
- 45. Buell J and Dawson-Hughes B(2010):** 25Hydroxy vitamin D, Dementia and Cerebral Vascular Pathology in Elders receiving Home Services. *Neurology*, 74: 18-26.
- 46. Annweiler C and Montero-Odasso O(2013):** Metanalysis of Memory and Executive Dysfunction in Relation to Vitamin D. *Journal of Alzheimer's Disease*, 37:147-171.