Examining the Association Between Vitamin D and Cognitive Disorders

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Introduction

Cognitive diseases, such as Alzheimer's Disease, are becoming increasingly common in the aging population. While there is currently no known cure for these diseases, there is evidence that suggests that vitamin D supplementation may help reduce the risk of cognitive decline, and even prevent these diseases from developing. Cognitive decline occurs when the brain's ability to deliberate and remember starts to decline. This can be caused by age-related degenerative brain diseases, including the aforementioned Alzheimer's and other forms of dementia, or by medical conditions that damage the brain, such as stroke or head trauma. Cognitive decline can also be caused by conditions that affect the brain's ability to use energy, such as depression, anxiety or chronic fatigue syndrome. It may be further aggravated by unhealthy lifestyles, such as smoking, poor nutrition, and lack of physical activity. This literature review will focus on exploring how vitamin D can help reduce cognitive disorders, focusing in particular on Alzheimer's disease in the aging population.

Age, Inflammation and Cognitive Decline

Several studies show that an increase in age directly correlates to cognitive decline. This correlation is depicted by displaying the consequences of age-related cognitive decline and describing the various domains of cognitive functioning that are affected by age-related decline, such as memory, processing speed, and executive functions (Salthouse, 2012). Age-related cognitive decline can lead to decreased functioning in everyday tasks, as well as decreased quality of life. Furthermore, it can also lead to an increased risk of developing various medical conditions, such as dementia and Alzheimer's disease (AD).

One of the root causes for age related cognitive decline is inflammation in the brain. Inflammation occurs when the body's immune system activates in response to injury, infection, or other types of stress. When inflammation occurs in the brain, it can cause damage to brain cells and disrupt normal brain function. Research suggests that inflammation may be a risk factor for developing AD (Sartori et al., 2012). A similar study done by Akiyama et al. shows that people with high levels of inflammation in the body, as measured by blood markers, are more likely to develop AD (Akiyama et al., 2000). Conversely, it has also been shown that people with Alzheimer's disease often have higher levels of inflammation in their brains compared to people without the disease (Kinney et al., 2018).

The set of studies above prove that cognitive impairment is undoubtedly one of the main symptoms of inflammation, and may begin to develop at a far younger age than it starts to show. Approximately 66% of Americans experience some level of cognitive impairment at an average age of approximately 70 years, but it is important to note that this is typically when symptoms become visible (Hale et al., 2020). The process of age-related cognitive decline begins much earlier than 60 years of age, and can even be decades earlier (Salthouse, 2009). Several common ailments including obesity, asthma, diabetes, arthritis and high blood pressure that afflict more than a billion people today in the world are associated with chronic inflammation and may therefore put these people at risk of developing cognitive disorders including AD. It is therefore important to understand how inflammation may lead to cognitive decline.

Beta Amyloid Plaques

There are several theories about how brain inflammation may contribute to the development of AD. One theory is that inflammation may lead to the accumulation of protein deposits called amyloid plaques and tau tangles in the brain, which are characteristic features of

AD (Haas and Dennis, 2007). The creation of Amyloid plaques can be explained, beginning with the Amyloid-β protein precursor (AβPP) which is broken down typically by two enzymes, namely beta-Secretase, and gamma-Secretase. This results in the formation of beta-Amyloids. Beta-Amyloid is produced by the body as a byproduct of normal metabolism, but in people with AD, it accumulates in the brain and forms amyloid plaques. These plaques are thought to interfere with the normal functioning of brain cells and contribute to the death of the brain (Castellani et al., 2010). These studies also describe two possible ways in which beta Amyloids cause damage to the brain. One possible way is that beta-Amyloids split and result in free radical release which damages neurons. Another possibility is that these beta-Amyloids result in tiny holes in membranes of neurons which results in unregulated calcium influx leading to neuron damage. These Amyloid plaques slowly accumulate in the brain as they cannot be broken down or removed and cause damage to the parts of the brain responsible for memory, including the entorhinal cortex and hippocampus, thus contributing to a number of neurodegenerative diseases (Haas and Dennis, 2007 and Castellani et al., 2010).

Beta-Amyloids are continuously produced and automatically cleared by various mechanisms in the brain for normal human beings. Beta-Amyloid turnover rate refers to the rate at which beta-Amyloid is produced and removed from the brain (Bateman et al., 2012). It depicts the balance between the production and clearance of beta-Amyloid. A study conducted by Patterson et al. examines the effects of age and beta-Amyloid turnover rate in the brain of Alzheimer's patients (Patterson et al., 2015). The study found that age is an important factor and that the rate of clearance decreased with increasing age. The study also suggested that age-related changes in brain physiology may contribute to the development of cognitive diseases, specifically AD.

In summary, beta-amyloid plaques are a key biomarker of AD and are caused by abnormal accumulation of beta-amyloids in the brain. These plaques cause damage to the brain cells and contribute to the development of the disease. The accumulation of these plaques is linked to brain inflammation and age-related changes in brain physiology and contributes to the development of cognitive diseases, specifically Alzheimer's.

Tau Tangles

In addition to amyloid plaques, another characteristic indicator of Alzheimer's disease is the formation of Tau tangles. Tau tangles or neurofibrillary tangles are aggregates of tau protein that are found in the brains of individuals with certain neurodegenerative disorders, such as AD, frontotemporal dementia, and Parkinson's disease (Haas and Dennis, 2007 and Castellani et al., 2010). In healthy neurons, tau normally binds to and stabilizes microtubules, which are structures that help route nutrients from the body of the cell to the axon and dendrites. The studies by Haas and Castellamni describe how in AD however, tau detaches from microtubules and sticks to other tau molecules, forming threads that eventually join to form tangles inside neurons. These tangles block the neuron's transport system, which harms the synaptic communication between neurons and eventually causes the neuron's death. The exact reason why tau tangles form is not fully understood, but it is thought to involve a combination of genetic and environmental factors. Some research, such as the study conducted by Poorkaj et al., suggests that certain genetic variations may increase the risk of developing tau tangles, while other research suggests that environmental factors, such as head injuries that result in inflammation, may also play a role (Poorkaj et al.,1998). A study by Ghosh et al. on rats suggested that an increase in Interleukin-1 beta (IL-1β), which is a type of cytokine, and

performs the role of stimulating inflammation in the body in response to infection and injury, resulted in exacerbation of tau pathology (Ghosh et al., 2013).

Another study by Liu et al. suggests that tau tangles may be related to oxidative stress, which is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify them. ROS are a byproduct of normal cellular metabolism and can cause damage to DNA, proteins, and lipids if they are not neutralized by the body's antioxidant defense mechanisms. Tau tangles may be the result of an accumulation of ROS-damaged tau protein in the brain. (Liu, 2015)

Overall, the exact cause of tau tangles is not fully understood and more research is needed to determine the factors that contribute to their formation. However, what is clear is that tau tangles lead to destruction of neurons and are typically found in individuals with certain neurodegenerative disorders.

Significance of Vitamin D

Vitamin D is a fat-soluble vitamin that is important for maintaining strong bones and teeth, as well as supporting immune function and regulating calcium and phosphorus levels in the body. It is produced in the skin in response to sunlight and gets finally converted into vitamin D3 or cholecalciferol through a process called isomerization. Vitamin D can also be obtained in the form of vitamin D2 (ergocalciferol) such as with supplements, fortified foods and in the form of vitamin D3 in animal products such as egg yolks and fish (Atli, 2018). Both vitamin D2 and D3 are converted to 25-hydroxyvitamin D (25(OH)D3) in the liver and this is the main form of vitamin D in the body and is used as a measure of vitamin D status(Farghali et al., 2020).

Vitamin D has been linked to a lower risk of cognitive decline in older adults and helps to regulate calcium absorption, which is important for proper functioning of the brain and nervous system (Kent et al., 2014). Higher 25(OH)D3 concentrations lowered dementia odds by 25% to 33% (Shea et al., 2022). Studies have found that low levels of vitamin D are associated with an increased risk of developing AD and other forms of dementia. One example of a study that portrays this relationship is a cohort study conducted in 2014 which discovered that lower levels of solar radiation were associated with increased odds of incident cognitive impairment (Kent et al., 2014). The study examined 19,896 cognitively intact black and white participants of ages 45 and above, and exposed the participants to several years of sunlight in order to find out the rate at which people cognitively decline. A telephone interview was conducted which recorded the participant's self-reported demographic and behavioral factors, and medical history. Participants were then visited in their homes by a trained health professional from Examination Management Services, Inc., who collected blood pressure, height, weight, venipuncture, urine, and conducted electrocardiograms. The participants were then exposed to varied amounts of sunlight for several different time intervals; from 1-year, all the way to 15-year time intervals. A year later, the participants were interviewed or examined again in order to determine the effects of the sun exposure on their cognitive impairment. The conclusion was that longer sunlight exposure, in other words an increase in vitamin D results in a decreased chance of contracting a cognitive disease.

Vitamin D has been scientifically proven to reduce the amount of Amyloid Protein in our brains. Yu et al. conducted a study on AβPP in transgenic mice, which found that a diet enriched with vitamin D led to a decrease in amyloid plaques in the brain of the mice (Yu et al., 2011). Specifically, the mice were fed a diet supplemented with either 2.5 or 5 μg/g of Vitamin D3 for

eight weeks. Results showed that the mice on the higher dose had a significant decrease in amyloid plaques in their brains compared to the control mice. The results of this study suggest that vitamin D may have a beneficial effect in reducing amyloid plaques in the brain, which may even provide insights into potential treatments for Alzheimer's and other cognitive diseases. Another study conducted by Babak et al. determined that higher vitamin D concentrations were associated with better cognitive performance and decreased risk of dementia and AD (Babak et al., 2014). This was determined through the correlation between vitamin D and $A\beta_{1-42}$ (a specific type of beta-Amyloid) in the cerebrospinal fluid (CSF), the volume of White matter (a type of brain tissue), and volumetric measures of several brain structures including structures of medial temporal lobe such as amygdala and hippocampus.

There is also some evidence to suggest that vitamin D may play a role in the development and progression of tau tangles. For example, a study published by Fan et al. recommends maintaining proper vitamin D levels is essential in the treatment of AD patients as vitamin D deficiency worsens AD-like pathologies by promoting inflammatory stress thereby increasing the production of beta-Amyloids and elevating Tau phosphorylation (Fan et al., 2020). Soares et al. conducted research on 100 cognitively impaired outpatient populations of age 65 years or older with a corresponding age and sex matched 76-person control group (Soares et al., 2022). This study proved that higher levels of 25(OH)D3 in CSF exhibited reduced levels of tau protein (t-tau) and phosphorylated tau protein (p-tau) in CSF. Higher levels of both t-tau and p-tau are typical markers for tauopathies, such as AD, and can be used to help diagnose these disorders.

Farghali et al. conducted a literature review on vitamin D supplementation to support brain health (Farghali et al., 2020). This study discusses research that proves that vitamin D decreases beta-Amyloid-peptide accumulation by stimulating phagocytosis and controlling the

transcription of Toll-like receptors and cytokines. In addition, vitamin D stimulates synthesis of Ca^{2+} ion binding proteins and provides neuroprotection since excess calcium leads to the formation of reactive oxygen species (ROS) which causes neuronal damage. Vitamin D's anti oxidative property further helps alleviate oxidative stress, which leads to neuronal cell death either via necrosis or apoptosis. Another study conducted by Almerighi et al. shows that vitamin D helps to inhibit the production of proinflammatory cytokines, which are proteins that play a key role in the inflammatory response (Almerighi et al., 2009). By inhibiting the production of these cytokines, vitamin D helps to reduce inflammation in the body which is known to be present in patients with cognitive disorders.

To summarize, vitamin D can be synthesized naturally by the body when exposed to sunlight as well as artificially ingested via food and supplements. The presence of vitamin D, specifically 25(OH)D3 in humans, lowers the risk of cognitive decline and dementia because of its properties including its ability to act as an anti-inflammatory and antioxidant. Therefore, vitamin D is vital in improving cognitive performance and preventing disorders like AD. Vitamin D also appears to be playing a beneficial role for people with cognitive disorders by helping reduce the amount of beta-Amyloid protein and thereby reducing amyloid plaques in the brain. Vitamin D may play a role in suppressing the progression of Tau tangles, which is another pathological hallmark of AD. The curative property of vitamin D may require further research and may even provide valuable insights into potential treatments for AD and other cognitive diseases.

Conclusion and Future Research

Examining existing literature, it is evident that age is the standout similarity factor among people with cognitive diseases. Damages happening in the brain typically are typically caused by

chronic inflammation and take several years or even decades before symptoms manifest. Old age seems to accelerate this process.

Diseases like AD have classic bio markers called Amyloid plaques which are caused by excessive accumulation of beta-Amyloid proteins. Chronic inflammation is one of the root causes resulting in beta-Amyloid protein accumulation (Sartori et al., 2012 and Akiyama et al., 2000). Another root cause is age-related defective transcription of immune genes necessary for phagocytosis resulting in improper clearance of beta-Amyloid proteins (Farghali et al., 2020). Tau tangles caused by Tau proteins is another. Tau, instead of attaching itself to microtubules (as it typically would), sticks to other tau molecules resulting in tangles inside neurons (Haas and Dennis, 2007 and Castellani et al., 2010). These tangles deposit and end up killing neurons by disrupting communication with other neurons. While the exact triggers for Tau tangles are still being researched, existing studies suggest inflammation, oxidative stress and genetic factors as possible root causes.

Vitamin D plays a vital role in maintaining cognitive health and reducing the risk of cognitive decline and dementia. Higher levels of vitamin D, specifically 25(OH)D3, have been linked to a lower risk of cognitive decline and dementia, and are associated with better cognitive performance (Kent et al.,2014 and Shea et al., 2022). Although the exact mechanisms behind how vitamin D may contribute to ameliorating cognitive disorders is unknown it is evident that vitamin D supplementation supports neuronal health because of vitamin D's 1) anti-inflammatory property (Almerighi et al., 2009) 2) ability to stimulate amyloid phagocytosis and clearance 3) ability to suppress APP transcription and 4) ability to prevent ROS (Farghali et al., 2020). Vitamin D supplementation could be the key ingredient that prevents multiple cognitive disorders and perhaps even reversing some of the effects. Therefore, maintaining

proper Vitamin D levels is essential for everyone including AD patients as Vitamin D deficiency worsens AD-like pathologies by promoting inflammatory stress.

Further research is recommended in understanding exactly how vitamin D prevents/reverses damages caused by cognitive disorders to substantiate correlation related studies. A longer-range study is also recommended to be conducted on several homogenous populations (same city, similar diet and sunlight exposure) starting at an age group of 45 years to understand the effect of vitamin D on cognitive health. Native vitamin D (cholecalciferol) is more bioavailable and has a longer half-life in the body compared to synthetic vitamin D (ergocalciferol). Native vitamin D also has a greater effect on calcium metabolism. Therefore, further analysis is recommended on the efficacy of synthetic vitamin D compared to native vitamin D so the right recommendations can be made for effectively combating cognitive disorders.

References

Akiyama, H et al. “Inflammation and Alzheimer's disease.” *Neurobiology of aging* vol. 21,3 (2000): 383-421. doi:10.1016/s0197-4580(00)00124-x

Almerighi, Cristiana et al. “1Alpha,25-dihydroxyvitamin D3 inhibits CD40L-induced pro-inflammatory and immunomodulatory activity in human monocytes.” *Cytokine* vol. 45,3 (2009): 190-7. doi:10.1016/j.cyto.2008.12.009

Atli Arnarson, "Vitamin D2 vs. D3: What’s the Difference?", Healthline - https://www.healthline.com/nutrition/vitamin-d2-vs-d3, March 4, 2018, Jan 2, 2023

Babak Hooshmand et al., “Vitamin D in Relation to Cognitive Impairment, Cerebrospinal Fluid Biomarkers, and Brain Volumes”, *The Journals of Gerontology: Series A*, Volume 69, Issue 9, September 2014, Pages 1132–1138, https://doi.org/10.1093/gerona/glu022

Bateman, Randall J et al. “Clinical and biomarker changes in dominantly inherited Alzheimer's disease.” *The New England journal of medicine* vol. 367,9 (2012): 795-804. doi:10.1056/NEJMoa1202753

Castellani, Rudy J et al. “Alzheimer disease.” *Disease-a-month : DM* vol. 56,9 (2010): 484-546. doi:10.1016/j.disamonth.2010.06.001

Fan, Yong-Gang et al. “Vitamin D deficiency exacerbates Alzheimer-like pathologies by reducing antioxidant capacity.” Free radical biology & medicine vol. 161 (2020): 139-149. doi:10.1016/j.freeradbiomed.2020.10.007

Farghali, Mahitab et al. “Can Brain Health Be Supported by Vitamin D-Based Supplements? A Critical Review.” *Brain sciences* vol. 10,9 660. 22 Sep. 2020, doi:10.3390/brainsci10090660

Ghosh, Simantini et al. “Sustained interleukin-1β overexpression exacerbates tau pathology despite reduced amyloid burden in an Alzheimer's mouse model.” *The Journal of neuroscience : the official journal of the Society for Neuroscience* vol. 33,11 (2013): 5053-64.

Haass, Christian, and Dennis J Selkoe. “Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide.” *Nature reviews. Molecular cell biology* vol. 8,2 (2007): 101-12. doi:10.1038/nrm2101

Hale, Jo Mhairi et al. “Cognitive impairment in the U.S.: Lifetime risk, age at onset, and years impaired.” *SSM - population health* vol. 11 100577. 31 Mar. 2020, doi:10.1016/j.ssmph.2020.100577

Kinney, Jefferson W et al. “Inflammation as a central mechanism in Alzheimer's disease.” *Alzheimer's & dementia (New York, N. Y.)* vol. 4 575-590. 6 Sep. 2018, doi:10.1016/j.trci.2018.06.014

Kent, Shia T et al. “The relationship between long-term sunlight radiation and cognitive decline in the REGARDS cohort study.” *International journal of biometeorology* vol. 58,3 (2014): 361-70. doi:10.1007/s00484-013-0631-5

Liu, Zhenzhen et al. “The Ambiguous Relationship of Oxidative Stress, Tau Hyperphosphorylation, and Autophagy Dysfunction in Alzheimer's Disease.” *Oxidative medicine and cellular longevity* vol. 2015 (2015): 352723. doi:10.1155/2015/352723

Patterson, Bruce W et al. “Age and amyloid effects on human central nervous system amyloid-beta kinetics.” Annals of neurology vol. 78,3 (2015): 439-53. doi:10.1002/ana.24454

Poorkaj, P et al. “Tau is a candidate gene for chromosome 17 frontotemporal dementia.” Annals of neurology vol. 43,6 (1998): 815-25. doi:10.1002/ana.410430617 https://pubmed.ncbi.nlm.nih.gov/35938253/

Salthouse, Timothy. “Consequences of age-related cognitive declines.” *Annual review of psychology* vol. 63 (2012): 201-26. doi:10.1146/annurev-psych-120710-100328

Salthouse, Timothy A. “When does age-related cognitive decline begin?.” *Neurobiology of aging* vol. 30,4 (2009): 507-14. doi:10.1016/j.neurobiolaging.2008.09.023

Sartori, Andrea C et al. “The impact of inflammation on cognitive function in older adults: implications for healthcare practice and research.” The Journal of neuroscience nursing: journal of the American Association of Neuroscience Nurses vol. 44,4 (2012): 206-17. doi:10.1097/JNN.0b013e3182527690

Shea, M Kyla et al. “Brain vitamin D forms, cognitive decline, and neuropathology in community-dwelling older adults.” Alzheimer's & dementia: the journal of the Alzheimer's Association, 10.1002/alz.12836. 7 Dec. 2022, doi:10.1002/alz.12836

Soares, Jelena Zugic et al. “Associations Between Intrathecal Levels of Vitamin D, Cytokines, and Core Biomarkers of Alzheimer's Disease: A Cross-Sectional Study.” Journal of Alzheimer's disease : JAD vol. 89,3 (2022): 825-834. doi:10.3233/JAD-220407

Yu, Jin et al. “Vitamin D3-enriched diet correlates with a decrease of amyloid plaques in the brain of AβPP transgenic mice.” *Journal of Alzheimer's disease : JAD* vol. 25,2 (2011): 295-307. doi:10.3233/JAD-2011-101986