Cognitive Consequences of Vitamin D Deficiency

BY RONALD DEVERE MD FAAN

I vividly remember (as may many of our readers), taking two tablespoons of cod liver oil every morning in the winter as a child growing up in Winnipeg, Manitoba, Canada in the late 40s through early 60s. The taste was horrible until the late 50s when it became available in an orange flavor. I was told that this cod liver oil was necessary to replace vitamin D levels, (needed for healthy bones) during the winter months when there was much less direct sunlight and less skin exposure because of the heavy winter clothing necessary for the Canadian Prairies. I don’t recall giving my children much cod liver oil or other forms of vitamin D when they were growing up in Houston.

My own experience seeing vitamin D blood levels measured in general medical practice over the last 50 years has been uncommon. But this has changed in the last three to four years. I have begun to see vitamin D levels reported in many routine lab tests (by family physicians) of many of my patients and in the last 15 months, I have included vitamin D levels in my evaluation of patients with memory and cognitive impairment. What has surprised many physicians including me is how frequently low vitamin D levels are recorded. My own vitamin D level was 18ng/ml, which is well below the recommended level of 30ng/ml or greater. This was especially surprising living in central and southeast Texas, which has a ton of sun most of the year. Plus, I drink milk and eat cereal which have Vitamin D added. Hypovitaminosis D has been shown to be common among older adults affecting up to 90 percent of the elderly population.1

It has only been around 25 years since the first report suggesting that the function of vitamin D extended well beyond its classic role in systemic calcium homeostasis.1 Vitamin D has been shown to influence (“neuroprotective”) neurogenesis, expression of neurotrophic factors, detoxification and amyloid beta clearance.23 Recent population based studies have consistently linked low Hydroxyvitamin D(25OHD3) levels to cognitive impairment in older adults in England,4 across Europe,5 and less consistent in United States.6

Before I begin discussing vitamin D and the central nervous system, let’s briefly review some basic physiology.

VITAMIN D: ORIGIN, METABOLISM AND BIOLOGICAL FUNCTION7

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. Ninety five percent 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.

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. equator), 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.

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 DBP. DBP 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. 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.

WHAT DOES “VITAMIN D DEFICIENCY” MEAN?

The best method to determine vitamin D status is to measure 25(OH)D blood levels. The Endocrine Society recommends the following guidelines for blood levels in adults and children.

- Vitamin D deficiency—20ng/ml or less
- Vitamin D insufficiency—21-29ng/ml
- Vitamin D sufficiency—30ng/ml or greater

VITAMIN D AND THE CENTRAL NERVOUS SYSTEM.

Much of the knowledge of the mechanism and biology of vitamin D in the brain initially came from lab rats and mice and many similarities were found in humans. Vitamin D receptors (VDR) as mentioned previously have been found throughout the human and rodent adult brain in the nuclei of microglia, astrocytes, oligodendrocytes and Schwann cells. Vitamin D has been shown to target genes in the brain. Gene products that have specific relevance to cognitive and behavioral function are:

- Neurotrophic growth factor (NGF) and brain derived neurotrophic factor (BDNF). NGF is present mainly in the hippocampus and neocortex which enhances neurotransmission (important areas for memory and executive function).
- BDNF affects survival and differentiation of dopamine cells. In 2008 McCann and Ames reviewed all the animal and human data on vitamin D and cognitive/behavior function. They stated that five criteria must be met linking the availability of vitamin D to cognitive and behavioral function in general:
  1. A plausible biological rationale
  2. A consistent association
  3. Specificity of cause and affect
  4. Dose response relationship (intensity of effect depends on degree of deficiency)
  5. Can experimentally manipulate the effect (reverse the affects)

They concluded that the main criterion most convincingly satisfied was number one: A plausible biological rationale. More work was needed to satisfy the other four criteria.

Since this paper, there has been a flurry of clinical studies on this topic. Recently, Annweiler, et al. in 2013 did a large meta-analysis of memory and executive dysfunction in relationship to vitamin D blood levels. These authors did a previous meta-analysis in 2009 and believed there was evidence of cognitive and behavioral impairment directly related to vitamin D levels, but were unable to determine which domain specific cognitive impairment was present (e.g. memory, executive function or both). They identified 285 papers on this subject matter and 48 met their inclusion criteria of: case control study, interventional study, data collection of serum Vitamin D and cognition as outcome, and adult human participants. Thirty-one out of forty-eight papers were eliminated because cognitive impairment did not study specific domains. The remaining 17 studies were thoroughly analyzed and included in their review and were all published in the last six years. Fifteen studies were from USA and Europe and two from Australia. Eleven studies were in older adults, four in middle age adults and one in younger adults. Data collection was based on cross sectional, prospective longitudinal and interventional studies. When regression models were performed, confounders considered were age, gender, BMI, ethnicity, education, incomes, health status, physical activity, mobility, renal function, alcohol, tobacco and caffeine use, season tested, and calcium, vitamin E and Zinc levels. Episodic memory was explored by verbal word list recall, serial digit, story and visual recall. Tests evaluating executive function included clock drawing, information processing speed, trail making test Part A, mental shifting and verbal fluency testing.

The meta-analysis provided evidence that low vitamin D is cross-sectionally associated in adults with impaired episodic memory and executive dysfunction, especially mental shifting, informational updating and processing speed. When the results were further analyzed with controls and including the confounders, episodic memory impairment did not reach statistical significance. They concluded that if they were to study a person chosen at random, that the probability was nine percent or less that the individual with high vitamin D levels would have a better score than an individual with a lower vitamin D level. The poor association between vitamin D levels and episodic memory is supported by an MRI study of older community members, who showed no changes to suggest hippocampal atrophy related to low vitamin D.

The correlation however between low vitamin D and executive function was statistically very positive. Individuals with high vitamin D levels taking into account all the cofounders and controls exhibited better executive function especially in mental shifting, information updating and processing speed, all very important as relates to reasoning, judgment, decision making and immediate recall (encoding). These areas of executive function depend on frontal–subcortical circuits and any lesions in these areas including vascular leads to impaired executive dysfunction. They stated that low vitamin D levels promotes increased stroke (white matter lesions) in these areas as reported in many imaging studies. Low vitamin D is strongly suggested to be a cardiovascular risk factor and promote onset of other vascular risk factors such as atherosclerosis, diabetes and hypertension. They also showed that low vitamin D levels precede decline of executive function and treating low levels of vitamin D were associated with improved executive function.
The single small placebo controlled trial which incorporated only younger adults did not find correlation between executive function and vitamin D levels. The authors of this meta-analysis had some very pertinent criticisms of the literature on this subject and suggested future recommendations:

- Not enough information to predict hypovitaminosis D related to cognitive impairment, and studies did not include a post-hoc power analysis. Equivocal or negative results could be results of small sample size.
- The heterogeneity of the studied population may also explain inconsistent results. Age has been shown to increase the risk of both cognitive decline and decreased vitamin D. Many of the studies included middle age and younger patients in various proportions, which can dilute the results in the older population of patients. Studies should focus on a homogeneous age group.
- Many studies with divergent results included only men or women. No evidence exists that vitamin D status is gender specific.
- Vitamin D receptor (VDR) genotype has not been addressed in most studies. VDR gene polymorphism may exist for responders and non-responders. Vitamin D regulates the expression of target tissues including the brain by binding the VDR's which are transcriptions factors regulating gene expression. It is possible that some allele combinations offer greater protection against cognitive decline in women compared to men or vice-versa.
- The methods for the determination of 25(OH)D levels were not standardized in many studies.
- Some trials used vitamin D2 supplements to treat low vitamin D levels, which has shown to be less efficient than D3 and often the follow-up duration of the study was very short (4-6 weeks).

Overall this critical analysis suggests future large carefully designed trials to examine the effects of vitamin D on cognition, especially executive function and memory, should consider a select population with low vitamin D levels such as older adults or disease specific population where low vitamin D is common and likely more responsive to vitamin D replacement.

**LOW VITAMIN D AND DEMENTIA**

Only a few articles have studied this topic. Annweiler, et al. 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, 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 (<10ng/ml) in 14.5 percent, and insufficient (< 10-20ng/ml) in 44 percent of participants. Twenty three percent developed dementia, one half were probable Alzheimer’s disease. There was a much higher prevalence of dementia among those with 25(OH) D insufficiency (<20ng/ml); 30 percent vs. 14 percent. These vitamin D deficiency levels were associated with increased white matter hyper-intensity and prevalence of white matter infarcts (10 percent vs. 7 percent). 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. 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.

**WHAT IS THE OVERALL MEANING OF THIS INFORMATION TO CLINICAL NEUROLOGISTS?**

1. Patients with progressive cognitive impairment, especially those 60 years and older should have a vitamin D level included in their lab work. In my practice, and I am sure most do, blood levels of Vitamin B12, folate, methylmalonic acid, homocysteine and TSH are regularly ordered if they were not previously done by other physicians.
2. To obtain the most information on an office cognitive test that includes executive function and reliable immediate and delayed memory testing, the Montreal Cognitive...
Assessment Test (MOCA) is by far the most reliable. The MMSE has little to no executive function and poor memory subtests. (Note: No office cognitive test score, especially if normal, should be relied on for cognitive capabilities without a thorough activities of daily living assessment, from the caregiver(s). Neuropsychological testing should be done when ADLs are impaired in normal or mildly low cognitive scores.)

3. A vitamin D level is expensive and it is important that the proper diagnostic code is used, otherwise it will not be covered by Medicare or other insurance. Diagnostic code 331.0, which is the code for dementia, usually covers the lab tests (B12, folate, MMA, homocysteine and TSH) but does not cover vitamin D levels. To get medical coverage for a vitamin D level, use code 268.9 (vitamin D deficiency). This has so far worked for us the last three months.

4. If the vitamin D level (25(OH) D) is under 30ng/ml, supplement with Vitamin D3 tablets, 2000 IU daily. Re-check vitamin D level in three months. Check cognitive office testing and ADL assessment with the caregivers to see if there is improvement with improved vitamin D levels. The data on low vitamin D reviewed, suggests that vascular disease in the brain, which is a common cause of cognitive impairment may stabilize or improve.

5. What if a patient only has memory loss or fits criteria for amnestic mild cognitive impairment (AMCI)? Even though the current literature has not shown any connection between low vitamin D and episodic memory loss, I would still measure a vitamin D level and treat it if it is low. There is nothing to lose because the cost of vitamin D3 supplement is very cheap. The jury is still out in regard to vitamin D and memory impairment and untreated may lead to future executive function impairment. Remember that many patients who have AMCI are in the multiple domain category, which may reveal executive function impairment that is not impairing ADLs. Many of these cases are more likely to develop dementia sooner than the single domain AMCI cases.

CONCLUSION AND SUMMARY

This paper has reviewed some important information about the role of vitamin D in cognitive and behavioral brain function. There are a number of suggested improvements in future studies. It appears that low vitamin D blood levels (below 30ng/ml) can impair executive function of the brain (vascular induced, and possibly other mechanisms outlined) related to genetic factors and gene expression and can improve when vitamin D3 supplementation is instituted. The lack of evidence suggesting memory impairment in low vitamin D levels should not be taken as a final conclusion. Hopefully future detailed improved studies will give us a more definite answer. It is strongly suggested that vitamin D blood levels be included in evaluating patients with cognitive impairment and if the level is low (below 30ng/ml) they should be treated with vitamin D3 supplementation and closely monitored.

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