Serum 25(OH)D and Cognition

Subjects: Nutrition & Dietetics

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Vitamin D, also referred to as serum 25(OH)D, reflects a group of fat-soluble steroids best known for increasing the intestinal absorption of minerals, specifically calcium, magnesium, and phosphate. The impact of serum 25(OH)D on skeletal diseases, such as rickets, has been well documented. There is growing appreciation for the role of vitamin D in cognition and potentially Alzheimer's disease.

Keywords: vitamin D ; cognition ; dementia ; obesity

1. Introduction

Dementia is a general term that describes a decline in mental ability severe enough to interfere with daily life. There is no cure for dementia; thus, it is imperative to identify strategies to prevent or slow the progression of this debilitating disease. Alzheimer's disease—the most common type of dementia—constitutes 60 to 70 percent of all dementia cases [1]. It is estimated that 50 million people worldwide are currently inflicted with dementia [1]. Mild cognitive impairment is considered a precursor to its Alzheimer's disease and is more common, effecting 15–20% of people age 65 or older [2].

Vitamin D, also referred to as serum 25(OH)D, reflects a group of fat-soluble steroids best known for increasing the intestinal absorption of minerals, specifically calcium, magnesium, and phosphate. The impact of serum 25(OH)D on skeletal diseases, such as rickets, has been well documented. Interestingly, there is growing appreciation for the role of vitamin D in cognition and potentially Alzheimer's disease [3]. Vitamin D metabolites, their related enzymes, and vitamin D receptors (VDR) have been found in the brain [3][4]. Specifically, they have been found in neurons and glial cells of the hippocampus, hypothalamus, cortex, and subcortex [4]. These are also areas in the brain known to be related to learning and memory. Alzheimer's disease is a neurodegenerative disease marked by consistent decline in cognition. The cause of Alzheimer's disease is unknown, however the possible association between Alzheimer's disease and vitamin D was first proposed in 1992 when decreased VDR levels in the hippocampus of patients with Alzheimer's disease were reported [3]. More recently, there have been genetic studies which document polymorphisms in the VDR which are related to an increase risk in poor cognition or development of Alzheimer's disease [3]. The Institute of Medicine (IOM) defines vitamin D insufficiency as a serum 25(OH)D level ≤20 ng/mL, based on the implication for bone health [5]. However, the Endocrine Society supports the view that a serum 25(OH)D ≤30 ng/mL is insufficient [6]. Applying the levels of the IOM (≤20 ng/mL), current estimates support that 39% of healthy adults in the US are vitamin D deficient [7]. When using the values set forth by the Endocrine Society (≤30 ng/mL), the number US adults with vitamin D deficiency increases to 64% [7]. Modifiable risk factors for vitamin D deficiency include decreased sunlight exposure, reduced dietary vitamin D intake, and obesity [8].

2. Current Insights on Serum 25(OH)D and Cognition

This research summarizes the literature to date on the associations between serum 25(OH)D and cognition in adults, controlling for the great variability in various assay methodology by limiting studies to those that use the recommended LC-MS assay for serum 25(OH)D determination. This topic is particularly relevant given the burgeoning aging population and the growing awareness between serum 25(OH)D and a variety of health outcomes. Reviews of this type are often difficult to perform, as the inherent purpose is to simplify findings from studies that possess highly variable research hypotheses, study designs and objectives. Studies reported a variety of aspects of cognition including: executive functioning, attention, working memory, information processing speed, verbal learning, and visual memory. Despite these differences, common themes emerged regarding the results and limitations (see **Table 1**).

Table 1. Key points regarding serum 25(OH)D and cognition.

- Observational studies support a significant association between low serum 25(OH)D and compromised cognition, which is further supported by the presence of VDR in neurons and glial cells of the hippocampus, hypothalamus, cortex, and subcortex.
- Data from randomized controlled trials is extremely limited, showing no evidence of cognitive improvements after short-term supplementation (4000–5000 IUs daily vs. 0–400 IUs daily) over 6–18 weeks.
- The MMSE was the most common cognition instrument used across studies, revealing inconsistent results.
- Sunlight, obesity and dietary supplementation are known determinants of serum 25(OH); however, these were not consistently collected or accounted for in analysis across studies
- The majority of studies included older participants, therefore it is difficult to make conclusions regarding the role of serum 25(OH)D in cognitive functioning in younger people
- Although minority populations are at risk for low serum 25(OH)D, the inclusion of these individuals is extremely limited.

First, although the methodology to measure serum 25(OH)D was consistent among all studies, the approaches to measure cognition were quite varied making it intrinsically difficult to draw definitive conclusions regarding the associations between serum 25(OH)D and cognition. Six of the thirteen studies used the MMSE to gauge cognitive function [9][10][11][12][13][14]; only two of these studies reported significant MMSE findings [11][15]. Additionally, two studies used a modified version of the MMSE (mMMSE) [15][16], so direct comparisons to other studies is limited. The mMMSE includes four additional test items and is designed to measure a broader variety of cognitive function thereby improving the instruments ability to detect cognitive impairment [17] While most of the studies used the MMSE to measure the outcome variable of global cognition, the study by Moon et al. (2015) [12] was slightly different from others. To ascertain a diagnosis of MCI or dementia, these investigators administered the MMSE, as a baseline measure of cognition. However, to measure cognition longitudinally the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Clinical Assessment Battery and the Korean version of the Mini International Neuropsychiatric Interview were used at baseline and follow-up visits. This approach allowed the authors to detect definitive diagnostic changes in cognition over time versus an overall global cognitive functioning ascertained when just the MMSE is used at one time point. Interestingly, seven of the studies that used the MMSE also administered at least one other instrument to measure cognition. Although only two studies reported significant findings with the MMSE, four studies reported significant findings when another instrumentation was used to measure cognition. For example, Brouwer-Brolsma et al. (2013) [9] and Brouwer-Brolsma et al. (2015) [10] had similar measures for cognition and both studies used a cognitive battery including digit span forward and backward test, Trail Making Tests A and B, Stroop Color–Word Test, the Verbal Fluency test, and the MMSE. Brouwer-Brolsma et al. (2015) [10] reported significant findings on Digit Span forward and backward and Brouwer-Brolsma et al. (2013) [9] reported significant findings on the Reaction Time Test, which was not used in Brouwer-Brolsma et al. (2015) [10] study. While these studies employed similar tools in similar populations, these inconsistencies may signify limitations in the instrumentation potentially diminishing or masking the links between cognitive functioning and serum 25(OH)D status.

To this end, Kueider et al. (2016) [13] and Milman et al. (2014) [11] also both used the MMSE to measure global cognition and the clock-drawing test to measure executive functioning; another aspect of cognition. The Clock-drawing Test has two parts as options when being administered. The first option is instructing the patient to draw a clock with the hands of the clock being set at ten past eleven, and the second part is where the patient is instructed to copy a picture of a clock with the hands being set at ten past eleven. Kueider et al. (2016) [13] reported significant findings on the command option of the clock-drawing test, but not the MMSE while Milman et al. (2014) [11] reported significant findings on the MMSE and the copy clock-drawing test. Perhaps the discrepancies in significant findings with the use of the MMSE relates to inherent restrictions of this measurement tool. Although the MMSE is widely used in longitudinal studies to track changes in cognition over time, ceiling/floor effects can lower the ability of the tool to measure true changes in cognition throughout the duration of a study [18], which would create a significant barrier to linking changes in cognition with serum 25(OH)D. The maximum MMSE score of 30 has been found to be easily obtained by participants with high levels of education and, likewise, the minimum score may be easily obtained by people with severely impaired cognition, making it impossible to

detect any improvement or decline in cognition over time in these participants [18]. Another limitation of the MMSE is the varied curvilinearity or sensitivity to change [18]. The psychometric property of curvilinearity reflects the concept that a change in the measurement tool many not represent the same intensity of cognitive change at all times [19]. Meaning, a 1-point change in the MMSE score from baseline to follow-up can have different meanings simply based on the initial score. These measurement difficulties with the MMSE can be more profound when using the tool to assess for changes in cognition in a sample of people that have varied levels of cognitive functioning. Taken together, these methodological challenges of quantifying cognition changes over time may have contributed to the differing documented significant findings on the impact of serum 25(OH)D on cognition in the studies reviewed. To combat these measurement problems, Philipps et al. (2014) [18] recommend a normalizing transformation analysis when using the MMSE to detect cognitive change and none of the studies reviewed performed the analysis in this manner. Given these challenges when using the MMSE to measure cognition over time, future research should use a battery of cognitive tests that are more sensitive to detecting changes in cognition over time. The Cambridge Neuropsychological Test Automated Battery (CANTAB) is an example of a battery that has been found to be reliable for use in patients with both mild cognitive impairment and Alzheimer's disease [20], and should be considered in studies going forward.

Second, obesity has long been considered a risk factor for vitamin D deficiency. Results from several large trials, including the National Health and Nutrition Examination Survey (NHANES) [21] and the Framingham Heart Study [22], have demonstrated an inverse relationship between serum 25(OH)D and BMI. That is, as BMI increases, serum 25(OH)D decreases. This concept is not new, but remains poorly understood. Cipriani et al. [23] proposes at least three mechanisms to explain this inverse relationship: (1) serum (OH)D moves out of circulation and is sequestered into the adipose tissue, (2) serum 25(OH)D potentially undergoes alterations in metabolism from hepatic steatosis; or (3) serum 25(OH)D is lowered in the blood due to the inhibitory effects of adipokines [23]. Further, low levels of serum 25(OH)D have been postulated to simply be a consequence of obesity-associated volumetric hemodilution [24]. Regardless of the etiology, the majority of studies did attempt to address the impact of obesity on vitamin D status by controlling for BMI during the analyses. Only three studies did not address obesity [25][26][27]. While BMI has been used a surrogate marker of adiposity for some time [28][29], a recent systematic review and meta-analyses of 31,968 healthy participants revealed that BMI fails to detect half of the people with excess adiposity [30]. Thus, its application as a surrogate marker for adiposity is questionable, underscoring the need to include more comprehensive methods to exam body composition going forward. This is especially relevant in studies addressing cognition, where study populations are typically older individuals and total adiposity increases while lean mass decreases. To more precisely capture body composition, the inclusion of dual-energy X-ray absorptiometry is recommended for future studies.

Third, sun exposure and dietary supplementation and, to a lesser extent, dietary intake are all major determinants of serum 25(OH)D levels [6]. Only six of the thirteen studies attempted to control for sun exposure and did so by including season of blood draw as a covariate in the analysis [9][10][14][15][16][31][32]. Although many older people spend a considerable amount of time indoors, it would be more methodically sound to gather data directly on time spent outdoors, especially during the summer months when the UV index is higher and translates to higher cutaneous conversion of vitamin D. Glanz et al. [33] developed a tool in 2008 to quantify sunlight exposure, sun protective practices, and skin pigmentation to address this concern in behavioral and intervention trials [33]. Further, none of the studies reporting significant associations between serum 25(OH)D and cognition collected information on dietary intake of vitamin D; however, three studies did gather data on vitamin D supplementation and control for this in the analysis [14][15][32]. Interestingly, two of the studies that measured vitamin D supplementation did not report a significant association between serum 25(OH)D and cognition [14] [32]. Therefore, the lack of information of vitamin D intake through diet or, more importantly, dietary supplementation is worrisome and needs stronger attention going forward. Rather than control for season of blood draw or ignore the important contributions of diet and supplementation, future studies should better quantify sunlight exposure and dietary intake, specifically focusing on vitamin D supplements and occult sources of vitamin D (e.g., combination calcium and vitamin D supplements).

Fourth, vitamin D deficiency is more prevalent among minority populations [34][35]. However, the populations were predominantly White. Two studies included race/ethnicity in their demographic explanations of the study populations, had exclusively White study participants [13][15], while five studies did not specify information regarding racial origins of the study population. Brouwer-Brolsma et al. (2013 & 2015) [9][10] recruited Dutch participants, Olsson et al. (2017) [14] included Swedish participants, the investigation by Milman et al. (2014) [11] was comprised of Ashkenazi Jewish participants, and Pettersen et al. (2017) [27] targeted participants from Northern British Columbia, Canada. Hence, it can be speculated that these were largely White participants. Persons of Hispanic origin were not represented in any of the aforementioned investigations. Given that both vitamin D deficiency and cognitive function are more prevalent in minority populations, this lack of diversity decreases the ability to generalize findings and determine the true implications of sufficient serum 25(OH)D levels on cognitive function.

3. Conclusions

Although all the studies meeting the inclusion criteria used the most accurate measure to determine serum 25(OH)D levels, the ability to make definitive conclusions regarding 25(OH)D and cognition remains hampered by several factors. The researchers hypothesize the reason for the difficulty in concluding the causal relationship between low serum 25(OH)D and cognition is the variation in study design, sample size, sample characteristics (e.g., age and race), and measures for cognition employed. First, observational study designs predominated over others; thus, determining the cause-and-effect relationship between serum 25(OH)D levels and cognition is simply not possible and the likelihood of reverse causality cannot be ruled out. Future studies should consider other study designs to efficiently and effectively evaluate this relationship. While a randomized controlled trial would be considered methodologically ideal, the length of time (e.g., decades) needed to determine changes in cognition may be financially impractical. A potential design consideration may include recruiting 'high risk' populations. Several gene mutations have been discovered in the last decade that can strongly predict early onset Alzheimer's disease [36]. Recruiting individuals with this genetic predisposition who possess low serum 25(OH)D levels presents an ideal opportunity to test the impact of vitamin D supplementation on cognitive decline. Rather than waiting decades to observe the outcome of interest, cognitive decline occurs more readily providing an efficient design in these vulnerable individuals, for whom the benefits could be quite tangible. In spite of this advantageous study design, determining the amount of vitamin D supplementation to provide remains controversial. Currently, the Institute of Medicine recommends no more than 4000 IU/day of Vitamin D_2 or D_3, reflecting the tolerable upper intake level [37]. However, recommendations of up to 6000 IU daily of vitamin D_2 or D_3 (or 50,000 IUs weekly for eight weeks) have been suggested [6]. Further, as previously mentioned, these two groups are not uniform in the cut-points used to define 'deficiency' (<20 ng/mL vs. <30 ng/mL, respectively). When considering the benign side effects of vitamin D supplementation and potential issues with daily pill compliance, recommendations of 6000 IUs per day and serum targets greater than >30 ng/mL seem practical and safe. Second, the validity of the instrumentation to discern a true relationship between serum 25(OH)D and cognition is concerning. Considerable efforts are needed to identify reliable and comprehensive tools to consistently measure cognition in a multitude of ways. The population that has been mostly studied is older in age, making generalizations on the impact of vitamin D on cognition to younger populations problematic. Finally, the populations who have been studied lack racial/ethnic diversity and, as such, it is difficult to generalize these findings to the populations that are most at risk for low serum 25(OH)D and cognitive dysfunction. Future investigations should include several tools to measures cognition and target Black and Hispanic participants. These measures will help broaden the knowledge and understanding of serum 25(OH)D deficiency and cognitive functioning, especially among vulnerable populations.

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