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Original Research

25-hydroxyvitamin D Levels are Associated with Cognitive Dysfunction in Type 2 Diabetes and the Metabolic Syndrome: A Preliminary Examination

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Abstract

***Background*:** Type 2 diabetes (T2DM) and metabolic syndrome are linked to pathological changes in the brain and increased likelihood of cognitive impairment. 25-hydroxyvitamin D insufficiency is commonly found in this population and is associated with cognitive dysfunction in other patient groups. This preliminary study sought to examine whether 25-hydroxyvitamin D levels are is associated with cognitive deficits in this population.

***Methods*:** Twenty individuals with T2DM and metabolic syndrome (n = 20, aged 45 to 72) were recruited for this cross-sectional study from a subspecialty diabetes center. All completed computerized cognitive testing and clinical evaluation, including assessment of circulating 25-hydroxyvitamin D values. Pearson correlations determined the association between 25-hydroxyvitamin D value and test performance.

***Results*:** Cognitive dysfunction was prevalent, as 45% met criteria for MCI and participants exhibited clinically meaningful deficits on an average of 2.4 +/- 2.0 tests. Lower levels of 25-

hydroxyvitamin D were associated with poorer performance on a measure of set shifting and psychomotor speed (i.e., Switching of Attention-Letters/Numbers, r=0.52, p <.0.05). Chi-square analyses showed that persons meeting criteria for MCI were more likely to have 25-hydroxyvitamin D levels </= 40 ng/ml ($\chi^2(1) = 2.78$, $p<0.05$; 88.9% vs 54.5%).

***Conclusions*:** Findings from this preliminary study suggest a possible relationship between lower 25-hydroxyvitamin D values and poorer executive function test performance in persons with type 2 diabetes and the metabolic syndrome. It is unclear if 25-hydroxyvitamin D directly affects cognition in this population, or if it serves as a proxy for another mechanism affecting cognition, such as poorer glycemic control or sedentary lifestyle. Prospective studies involving supplementation may help to clarify the role of 25-hydroxyvitamin D in cognition for this population.

Keywords

25-hydroxyvitamin D; cognition; metabolic syndrome

1. Introduction

Type 2 diabetes (T2DM) and metabolic syndrome elevate risk for Alzheimer's disease and stroke, but are also linked to cognitive impairment and pathological brain changes prior to the diagnosis of these neurological disorders [1]. Early identification of modifiable risk factors for cognitive dysfunction in this population is important. Among many others, insufficiency of the neurosteroid hormone 25-hydroxyvitamin D is one possible contributor to cognitive impairment. Accumulating evidence demonstrates a relationship between 25-hydroxyvitamin D and neuronal integrity and transmission [2]. 25-hydroxyvitamin D receptor is expressed in multiple regions of the brain, such as the prefrontal cortex, basal ganglia, and hippocampus [3] that are crucial for cognition. Low 25-hydroxyvitamin D values are associated with cognitive deficit and linked to cognitive decline [4].

It is also possible that 25-hydroxyvitamin D impacts cognitive function through indirect pathways. Reduced 25-hydroxyvitamin D is also independently associated with insulin resistance [4] and correction of insufficient 25-hydroxyvitamin D via dietary supplementation improves glycemic control, including insulin sensitivity [5]. If cognitive impairment in those with T2DM and metabolic syndrome is partially due to 25-hydroxyvitamin D insufficiency, supplementation may be an alternative treatment for both physical and cognitive symptoms.

Despite previously demonstrated links, no prior work has examined the relationship between 25-hydroxyvitamin D and cognitive performance in this population. The current study sought to clarify the presence of cognitive deficit in individuals with T2DM and metabolic syndrome and to determine if low 25-hydroxyvitamin D is associated with greater cognitive impairment. We predicted that cognitive impairment would be prevalent in this sample, and linked to lower 25-hydroxyvitamin D.

2. Materials and Methods

2.1 Participants

A convenience sample of 20 patients (45-72 years), with T2DM and metabolic syndrome meeting inclusion/exclusion criteria were recruited from the Cleveland Clinic Diabetes Center and consecutively enrolled for this cross-sectional study from June-December 2012. Inclusion criteria were diagnoses of both T2DM and metabolic syndrome, available 25-hydroxyvitamin D level information, and English-speaking. Metabolic syndrome was defined using the National Cholesterol Education Program criteria [NCEP, 2001], based on presence of three or more of the following: increased waist circumference (>102cm for men/>88cm for women); elevated triglycerides (≥150 mg/dl); low HDL cholesterol (<40 mg/dl in men/<50 mg/dl in women); hypertension (≥130/≥85 mmHg); and impaired fasting glucose (≥110 mg/dl). Exclusion criteria were: history of neurologic disorder or injury, moderate to severe head injury, severe psychiatric illness, alcohol or drug abuse, learning disorder or developmental disability, or impaired sensory function precluding computerized testing. See Table 1 for demographic and medical characteristics.

As noted in Table 1, participants had an average of 34.6 ± 12.4 ng/ml for 25-hydroxyvitamin D. Two individuals had levels < 20 ng/ml and 40% had levels < 40 ng/ml. No participant was on a 25-hydroxyvitamin D supplement at the time of cognitive testing, though 6 individuals reported taking a multi-vitamin as part of their clinical visit. Notably, such persons did not differ in their observed 25-hydroxyvitamin D levels (39.82 ± 8.01 vs. 32.37 ± 13.52; t (18) = 1.25, p = .23).

All study methods were approved by the local Human Subjects Protection Board prior to initiation of activities.

Table 1 Demographic and medical characteristics of 20 adults with type 2 diabetes and metabolic syndrome

25-hydroxyvitamin D (ng/ml)	34.6 ± 12.4
Age mean (SD) (years)	61.7 ± 7.5
Males (%)	40.0%
Hypertension (%)	90.0%
Hyperlipidemia (%)	85.0%
Hemoglobin A1c (%)	7.2 ± 1.8
HDL (mg/dl)	45.0 ± 14.6
LDL (mg/dl)	92.6 ± 25.3
Body mass index (kg/m^2)	35.0 ± 11.4

2.2 Instrumentation

2.2.1 Demographic and Medical History. Participant self-report and electronic medical records provided demographic and medical/health variables.

2.2.2 Physical Measures. Body mass index and blood pressure were measured immediately prior to cognitive testing. Blood draw for 25-hydroxyvitamin D (ng/ml) was completed within 2 weeks of the cognitive testing session. Blood assays were conducted as part of standard clinical care through the Cleveland Clinic Reference Laboratory using a chemiluminescent assay (DiaSorin, Stillwater, MN). Values were extracted from electronic medical records at the time of the current study.

2.2.3 Cognitive Function. Cognitive performance was measured via Webneuro, a computerized measure that assesses multiple cognitive domains [6]. Performances are standardized using normative data from the Brain Resource International Database (BRID; www.brainnet.net) matched for age, gender, and estimated intelligence. We have used these tasks in our prior work with T2DM, and tasks have been previously described [7], including Digit Span, Switching of Attention, Verbal Interference, Mazes, and Verbal Memory. A deficit was defined in accordance with standard clinical practice as performance greater than one standard deviation below the mean.

2.3 Procedures

Participants were recruited from a subspecialty diabetes center at a tertiary referral center on a voluntary basis. They were approached by research team members upon arrival for a clinical appointment and provided with information about study activities. After providing written informed consent, participants completed the computerized cognitive testing and granted access to their electronic medical record.

2.4 Power Analysis

A priori power calculation for tests of association to detect a moderate bivariate correlation (r=.30) indicated that a sample size of 16 would provide 80% power to detect significance. The sample size of 20 was derived as a conservative approach for detecting meaningful correlations.

2.5 Statistical Analyses

Descriptive statistics characterized the sample, including demographic/medical variables and cognitive function performance. Mean imputation was used to generate cognitive test performance for a participant based on a linear combination of performance on all other cognitive tests (correlation between predicted and observed values in other participants, r = 0.97). Pearson correlations determined the association between 25-hydroxyvitamin D value and test performance. Chi-square analyses examined the possible association between meeting established criteria for mild cognitive impairment (MCI; >1 SD below normative performance on two or more tests within a cognitive domain [8]) and 25-hydroxyvitamin D levels <40 ng/ml.

Consistent with the exploratory goals of this preliminary study, one-tailed significance testing was utilized.

3. Results

3.1 Prevalence of Cognitive Dysfunction

Cognitive dysfunction was prevalent, as 45% met criteria for MCI and participants exhibited clinically meaningful deficits on an average of 2.4 +/- 2.0 tests. Impaired test performances were particularly common on tests of attention and executive function (range from 25-50%), though less frequent on measures of learning/memory (10-15%). See Table 2.

Table 2 Prevalence of cognitive dysfunction

Domain/Test	% impaired
Attention	
Digit Span	30.0
Working Memory Reaction Time	50.0
Verbal Interference-Word	25.0
Executive Function	
Verbal Interference-Color Word	45.0
Switching of Attention-Letters/Numbers	35.0
Maze Errors	30.0
Memory	
Sum of Learning Trials	10.0
Recognition	15.0

Note. % impaired defined as % of sample scoring >1 SD below normative performance based on age, gender, and estimated IQ;

3.2 25-hydroxyvitamin D and Cognitive Function

Pearson correlations showed lower levels of 25-hydroxyvitamin D were associated with poorer standardized performance on a complex measure of set shifting and psychomotor speed (i.e., Switching of Attention-Letters/Numbers, $r=0.52$, $p < .0.05$). See Table 3. Chi-square analyses also showed that persons meeting criteria for MCI were more likely to have 25-hydroxyvitamin D levels < 40 ng/ml (as per [9]; χ^2 (1) = 2.78, $p<0.05$; 88.9% vs 54.5%).

Table 3 Pearson correlations between cognitive test and 25-hydroxyvitamin D levels in the full sample

Domain/Test	r
Attention	
Digit Span	0.00
Working Memory Reaction Time	0.35
Verbal Interference-Word	-0.06
Executive Function	
Verbal Interference-Color Word	0.23
Switching of Attention-Letters/Numbers	0.52*
Maze Errors	0.33
Memory	
Sum of Learning Trials	0.22
Recognition	0.21

Note. % impaired defined as % of sample scoring >1 SD below normative performance based on age, gender, and estimated IQ; *indicates p<.05

5. Discussion

The current study examined the prevalence of cognitive impairment in individuals with T2DM and metabolic syndrome and sought to determine whether 25-hydroxyvitamin D is linked to dysfunction. Results indicate high prevalence of cognitive impairment in attention and executive function, though memory deficits were less common. Lower 25-hydroxyvitamin D was associated with poorer performance on a measure of executive function and associated with greater likelihood of meeting criteria for MCI.

Cognitive dysfunction is common in both T2DM [10] and metabolic syndrome [11] and the current findings suggest that persons meeting criteria for both conditions may be especially likely to exhibit impairment on testing. Past research has also found that cognitive impairment (as defined by a broadband screening measure) in individuals with T2DM is associated with insufficient 25-hydroxyvitamin D [12]. Consistent with expectations and past findings, a positive association between 25-hydroxyvitamin D and cognition was noted in the current sample, though only executive function demonstrated this relationship. Many of the brain regions involved in 25-hydroxyvitamin D signaling are integrated within the frontal systems, including the prefrontal cortex and basal ganglia [5], which underlie executive functions. If involved in neuronal integrity

and transmission [3] in these regions, 25-hydroxyvitamin D could exert direct effects on executive function. Given the hippocampal involvement in 25-hydroxyvitamin D signaling and memory, the lack of relationship between these variables is surprising, though this may be due to restricted range, as relatively few individuals demonstrated impairment in memory. Replication in a larger sample with greater variability in cognitive function (e.g, persons with Alzheimer's disease or amnestic MCI) would more clearly establish the relationship between 25-hydroxyvitamin D and cognition in this population.

The current results demonstrate a relationship between 25-hydroxyvitamin D and cognition in this population, but do not address causation. It is unclear if 25-hydroxyvitamin D directly impacts cognition via above-described mechanisms, or if it serves as a proxy for another mechanism. For example, better glycemic control is positively associated with better cognition [13] and higher 25-hydroxyvitamin D [4] in individuals with T2DM, thus the relationships observed in the current sample could be influenced by glycemic control. Similarly, low levels of physical activity, common in this population, are associated with reductions in cognitive performance [14], and a sedentary lifestyle may translate into reduced sun exposure. Prospective studies examining the interrelationship among risk factors for cognitive impairment and intervention are needed.

Limitations of this study suggest directions for future research. A primary limitation of the current study is the absence of a matched control group. Though the current methodology is appropriate for a preliminary study, future work that includes comparison groups such as healthy older adults and persons with only T2DM or metabolic syndrome are needed to clarify whether the observed relationships are specific to persons with comorbid T2DM and metabolic syndrome. Similarly, the current study cannot determine the extent to which the association between 25-hydroxyvitamin D and cognitive function in independent of other factors. For example, indices for obesity, hypertension, and insulin resistance are known to be associated with poorer cognitive outcomes [12, 15] and their specific and combined influence on the current findings is unclear. Prospective studies utilizing 25-hydroxyvitamin D supplementationmay answer the question of causality, particularly if controlling for abnormalities in glucoregulation. Additionally, although our small sample size provided adequate power to detect the current findings, replication with a larger sample, accounting for variables not examined (e.g., calcium) is needed.

In summary, this preliminary study found 45% of persons with T2DM and metabolic syndrome met criteria for MCI and that lower 25-hydroxyvitamin D levels were associated with greater impairment on objective neuropsychological testing. Although 25-hydroxyvitamin D may exert direct effects on cognition, it is possible that it reflects another factor, such as glycemic control or sedentary lifestyle. Prospective supplementation studies are needed to determine if causation may be attributed to 25-hydroxyvitamin D in cognition for this population and to the extent to which it may be modifiable.

Author Contributions

This manuscript meets the Committee on Publication Ethics standards for authorship credit. All authors gave approval of the final version to be published. Specific contributions are:

- Lisa Manderino was responsible for data interpretation and primary drafting of the manuscript.

- Mary Beth Spitznagel was responsible for data interpretation and contributed to drafting of the manuscript.
- Divya Yogi-Morren was responsible for acquisition of data and critical revision of the manuscript.
- John P. Kirwan made substantial contributions to conception and design, and was responsible for critical revision of the manuscript.
- Sangeeta Kashyap made substantial contributions to conception and design, and was responsible for acquisition of data and critical revision of the manuscript.
- John Gunstad made substantial contributions to conception and design, and was responsible for data analysis and interpretation, as well as critical revision of the manuscript.

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Competing Interests

The authors have declared that no competing interests exist.

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