

The effect of vitamin D on cognitive functions in young female patients: a prospective controlled study using the Montreal Cognitive Assessment

O efeito da vitamina D nas funções cognitivas em pacientes jovens do sexo feminino: um estudo prospectivo controlado usando a avaliação cognitiva de Montreal

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ABSTRACT

Aim: Our aim was to determine whether there is a relationship between vitamin D [25(OH)D] and cognitive functioning in women with low 25(OH)D levels. **Methods:** Ninety female patients, 25–45 years of age, who attended our outpatient clinic and had 25(OH)D levels < 30 ng/mL, were included. The Montreal Cognitive Assessment (MoCA) scale was used to determine cognitive functioning; the scale is divided into seven subgroups. Patients were divided into three subgroups according to their 25(OH)D levels. After a three-month period of 25(OH)D replacement, the patients underwent a re-evaluation using the MoCA scale. **Results:** The total MoCA score before treatment was significantly different from the score after treatment ($p < 0.05$). Language and delayed recall functions were significantly different before and after treatment ($p < 0.05$). **Conclusion:** Vitamin D levels were related to cognitive functioning in our study group.

Keywords: Vitamin D; cognition; Montreal cognitive assessment.

RESUMO

Objetivo: Nosso objetivo foi determinar se existe uma relação entre a vitamina D [25(OH)D] e o funcionamento cognitivo em mulheres com baixos níveis de 25(OH)D. **Métodos:** Noventa pacientes do sexo feminino (25-45 anos de idade) que se apresentaram ao nosso ambulatório e tinham níveis de 25(OH)D <30 ng/mL foram incluídas. A escala de avaliação cognitiva de Montreal (MoCA) foi usada para determinar o funcionamento cognitivo; a escala é dividida em sete subgrupos. As pacientes foram divididas em três subgrupos de acordo com seus níveis de 25(OH)D. Após um período de três meses de reposição de 25(OH)D, as pacientes foram submetidas a uma reavaliação de acordo com a escala MoCA. **Resultados:** O escore total da MoCA antes do tratamento foi significativamente diferente do escore após o tratamento ($p < 0,05$). As funções de idioma e recordação atrasada foram mais significativamente diferentes entre antes e depois do tratamento ($p < 0,05$). **Conclusão:** O nível de vitamina D foi relacionado ao funcionamento cognitivo em nosso grupo de estudo.

Palavras-chave: Vitamina D; cognição; Testes de estado mental e demência.

Vitamin D (25-hydroxy vitamin D [25(OH)D]) is a steroid hormone with a variety of physiological roles. In addition to its well-known role in calcium homeostasis, several more-recent publications have indicated that vitamin D deficiency can lead to deficits in neurocognitive functioning¹. The relationship between vitamin D and central nervous system functioning has been investigated for many years. It is known that the enzyme responsible for synthesizing the vitamin D receptor and the active form of 25(OH)D are present in the central nervous system². Moreover, 25(OH)D increases

gamma glutamyl transpeptidase and glutathione, and glutathione is a natural antioxidant that protects the integrity of the neurotransmitter pathway critical for oligodendrocytes and mental processes³. The 25(OH)D regulates neuronal calcium homeostasis and protects neurons from excessive calcium intake⁴. A reduction in 25(OH)D concentration has been associated with a decline in cognitive functioning, as well as impaired cognitive functions such as memory, orientation^{5,6,7,8}, and executive functions^{9,10} in patients with dementia and Alzheimer's disease¹¹.

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Previous studies have generally been conducted in groups of individuals of an older age; data on younger individuals are limited, and subgroups have not been precisely evaluated^{9,12,13,14,15}. The main question about 25(OH)D and cognitive dysfunction is whether a vitamin D deficiency impairs cognitive functions. This study elucidated the causal contribution of 25(OH)D to outcomes related to cognitive functioning and determined whether 25(OH)D replacement therapy affects functioning in these domains. We prospectively investigated whether there is a correlation between 25(OH)D and cognitive functioning in young female patients with a 25(OH)D deficiency, and whether there is a difference in cognitive functioning after 25(OH)D replacement.

METHODS

Female patients (aged 25–45 years of age) who were admitted to the physical therapy and rehabilitation outpatient clinic between May 2017 and September 2017, who had a low 25(OH)D < 30 ng/ml, did not complain of cognitive dysfunction, and scored < 10 points on the Beck Depression Inventory, were included in the study. The demographic data, age, and educational level of the patients were recorded. Calcium, phosphorus, magnesium, 25(OH)D, and parathyroid hormone values were measured. The patients were divided into three groups according to their 25(OH)D level: < 10 ng/mL (group 1, n = 30), 10–20 ng/mL (group 2, n = 30), and 20–29 ng/mL (group 3, n = 30). The Montreal Cognitive Assessment (MoCA) scale was used to assess cognitive functioning. The scale is divided into seven subscales. The participants were treated according to their low 25(OH)D levels¹⁶. We treated all adults who were vitamin D deficient with 50,000 IU of vitamin D, once a week for eight weeks, to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 1,500–2,000 IU/d. The participants were re-evaluated three months later using the MoCA scale.

Exclusion criteria

We excluded patients with autoimmune and chronic inflammatory diseases (rheumatoid arthritis and ankylosing spondylitis etc), chronic systemic diseases (chronic renal failure and liver disease etc), known malabsorption (celiac sprue or radiation enteritis etc), active infection, cancer, thyroid/parathyroid disease, low vitamin B12 level, history of a neurological disease, psychiatric disorder history (depression, anxiety, psychosis, schizophrenia, bipolar disorder etc), glucocorticoid use, hormone replacement, antiepileptic drug use, cerebrovascular accident, central nervous system tumors, head trauma, multiple sclerosis, epilepsy, movement disorders or migraine treatment, current or recent history of dependence on alcohol or illicit substances, intellectual disability, sleeping problems, pregnancy, and fibromyalgia.

This study was approved by the Ethics Review Board of Bozok University, Faculty of Medicine (no: 2017/01-05/30). Written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Serum 25(OH)D measurement

Serum 25(OH)D levels were measured with the Architect i2000 (Abbott, Diagnostics, Wiesbaden, Germany) operating with the use of chemiluminescent microparticle immunoassay technology. The linearity of assay was 3.4–155.9 ng/ml. The manufacturer reports an intra-assay precision of 2.3%, 2.1%, 2.8% and a total precision of 3%, 3.1%, 4.1% for values 20, 40, 78.3 ng/dl (respectively). Serum 25(OH)D levels < 10 ng/ml were considered a severe deficiency, 10–20 ng/ml was considered a deficiency, 21–29 ng/ml was considered an insufficiency, and ≥ 30 ng/ml was considered sufficient. Measurements of serum 25(OH)D levels are considered the best indicator to assess the overall vitamin D profile¹⁶.

Montreal Cognitive Assessment

The MoCA was developed as a rapid screening test to assess mild cognitive impairment¹⁷. This test evaluates seven different cognitive functions, including attention and concentration, executive functions, delayed recall, language, visuospatial construction, abstract (conceptual) thinking, and orientation to time and place. The MoCA takes about 10 minutes to complete. The highest total score on the test is 30 points, and ≥ 21 points is considered normal. A Turkish validity and reliability study has been conducted¹⁸.

Montreal Cognitive Assessment assesses the following:

- 1) The short-term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately five minutes;
- 2) Visuospatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point);
- 3) Multiple aspects of executive functions are assessed using an alternation task adapted from the Trail Making B task (1 point), and a phonemic fluency task (1 point);
- 4) Two-item verbal abstraction task (2 points);
- 5) Attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each);
- 6) Language is assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points), and the aforementioned fluency task;
- 7) Orientation to time and place (6 points).

Statistics

The distribution of MoCA scores was not homogeneous, so the differences between the groups were assessed by the nonparametric Mann–Whitney U and chi-square tests. The

results are reported as mean \pm standard deviation or as percentages. Differences among the groups were tested with analysis of variance. A *post-hoc* test was used to determine from which group the difference originated. The paired sample t-test was used for each group in the before-treatment and after-treatment comparisons. A p-value < 0.05 was accepted as significant. The statistical analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

In total, 90 female patients with the mean age of 37 years (min: 29 – max: 44) (group 1), 38 years (min: 25 – max: 45) (group 2), 37 years (min: 26 – max: 45) (group 3) were included.

No significant differences in the demographic data or blood levels, except 25(OH)D levels, were observed among the groups ($p > 0.05$) (Table 1). The 25(OH)D levels of each group are shown in Table 2. The mean before and after treatment MoCA values of the groups were within the normal limits in separate and total points (Table 3).

A significant difference was found when the before treatment and after treatment MoCA total scores of the three groups were compared ($p < 0.05$, $p < 0.001$, respectively) (Table 3). No differences were observed among the groups in terms of attention, conceptual thinking, executive function, or orientation before and after treatment ($p > 0.05$). Language and delayed recall functions were significantly different before and after treatment ($p < 0.05$) (Table 3).

A significant difference was found between group 1 and groups 2 and 3 in the MoCA total score before treatment ($p < 0.05$), but no significant difference was observed between the groups after treatment ($p > 0.05$) (Table 4).

DISCUSSION

This is the first study, to our knowledge, evaluating the effects of 25(OH)D replacement in adult females in terms of key cognitive measures by MoCA. In our study, the MoCA scores of all participants were within the normal limits. However, we found a significant difference in the total MoCA scores before treatment and after treatment in all three groups and more significantly in language and delayed recall as a subgroup. Some studies¹¹ have shown that a low concentration of 25(OH)D could be effective in diseases, such as dementia and Alzheimer's disease at later ages, as well as in cognitive dysfunction, such as memory and orientation^{5,8} and executive dysfunction^{9,10}, but it is not exactly clear whether the concentration of 25(OH)D actually alters cognitive functioning.

Jorde et al.¹³ demonstrated an average of 5% better performance on tests in participants older than 65 years, but did not find a correlation between 25(OH)D levels and cognitive function test scores in individuals younger than 65 years of age (mean age: 57 years). They divided the patients into four groups according to their 25(OH)D level, and did not find any difference between the groups. A population comprising male and female participants,

Table 1. Demographic properties and laboratory findings of the patient.

Variable	Group 1 (vitamin D < 10 ng/mL) n = 30	Group 2 (vitamin D = $10 - < 20$ ng/mL) n = 30	Group 3 (vitamin D = $20 - < 29$ ng/mL) n = 30	Total n = 90	p-value
Age	37.07 \pm 4.5	38.13 \pm 5.9	36.83 \pm 5.4	37.26 \pm 5.3	0.73 ^F
Education n (%)					
Middle school	17 (43.6)	11 (28.2)	11 (28.2)	39(100)	
High school	9 (27.3)	12 (36.4)	12 (36.4)	33(100)	0.49 ^{CST}
University	4 (22.2)	7 (38.9)	7 (38.9)	18(100)	
25(OH)D (ng/mL)	5.95 \pm 1.9	15.16 \pm 2.7	22.70 \pm 1.9		0.02*
PTH (pg/mL)	90.43 \pm 11.8	72.29 \pm 20.3	71.94 \pm 18.9		0.45
Ca (mg/dL)	9.37 \pm 0.4	9.53 \pm 0.4	9.20 \pm 1.8		0.49
Phosphorus (mg/dL)	2.21 \pm 0.5	2.12 \pm 0.4	2.25 \pm 0.4		0.79
ALP (U/L)	63.90 \pm 15.4	68.07 \pm 15.5	65.30 \pm 19		0.50

Data are expressed as mean \pm standard deviation, or the number (percentage) of cases; F: ANOVA: analysis of variance; CST: Chi-square test; *Statistical significance: $p < 0.05$; ALP: Alkaline phosphatase; PTH: Parathyroid hormone; Normal ranges: calcium; 8.8-10.6 mg/dL, phosphorus; 2.5-4.5 mg/dL, ALP: 30-120 U/L, PTH; 12-88 pg/mL, 25(OH)D > 30 ng/mL.

Table 2. Vitamin D levels of each group.

Vitamin D	Group 1 X \pm SD	Group 2 X \pm SD	Group 3 X \pm SD	Total X \pm SD
Before treatment	5.95 \pm 1.95	15.16 \pm 2.76	22.98 \pm 1.91	14.69 \pm 7.34
After treatment	45.07 \pm 8.37	50.22 \pm 6.55	52.42 \pm 5.50	49.24 \pm 7.50
Test*	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$

*Paired T test; statistical significance $p < 0.05$.

nearly half of whom were college graduates, was assessed by the Mini Mental State Examination. Unlike that study, our participants comprised younger age groups, and we found a significant difference in the total scores of all participants, and in the post-replacement MoCA scores of the subgroups.

Dean et al.¹⁴ divided healthy young subjects with normal 25(OH)D levels (mean ages: case group: 21 years, control group: 22 years) into two groups and provided 25(OH)D supplementation to one group for six weeks while the other

group received a placebo. At the end of six weeks, they did not find a significant change in cognitive functioning between the groups, indicating that 25(OH)D supplementation had no effect on cognitive function. However, Dean et al.¹⁴ designed the study with participants with normal 25(OH)D levels. The 25(OH)D levels of the patients who participated in our study were low. The MoCA scores of the participants were within the normal range, but a significant difference was found between the initial values and the post-replacement scores.

Table 3. The means of MoCA scores before and after treatment of groups.

MoCA Subgroups	Group 1	Group 2	Group 3	Total MoCA
	X ± SD	X ± SD	X ± SD	X ± SD
Visual Structuring				
Before treatment	3.33 ± 0.75	3.60 ± 0.67	3.83 ± 0.37	3.59 ± 0.65
After treatment	3.83 ± 0.37	4.0 ± 0.00	3.8 ± 0.37	3.93 ± 0.25
Test*	p = 0.001	p = 0.003	p = 1.000	p < 0.001
Language				
Before treatment	4.10 ± 0.54	4.30 ± 0.53	4.57 ± 0.50	4.32 ± 0.55
After treatment	4.33 ± 0.54	4.50 ± 0.50	4.73 ± 0.45	4.52 ± 0.52
Test*	p = 0.01	p = 0.01	p = 0.02	p < 0.001
Executive Functions				
Before treatment	1.53 ± 0.62	1.53 ± 0.50	1.27 ± 0.64	1.44 ± 0.60
After treatment	1.73 ± 0.45	1.80 ± 0.40	1.70 ± 0.46	1.74 ± 0.43
Test*	p = 0.08	p = 0.009	p = 0.002	p < 0.001
Time/Place Orientation				
Before treatment	6.0 ± 0.0	6.0 ± 0.0	5.97 ± 0.18	5.99 ± 0.10
After treatment	6.0 ± 0.0	6.0 ± 0.0	6.0 ± 0.0	6.0 ± 0.0
Test*	¥	¥	p = 0.32	p = 0.32
Conceptual Thinking				
Before treatment	1.13 ± 0.62	1.07 ± 0.58	1.20 ± 0.66	1.13 ± 0.62
After treatment	1.20 ± 0.55	1.20 ± 0.61	1.40 ± 0.62	1.27 ± 0.59
Test*	p = 0.42	p = 0.25	p = 0.05	p = 0.02
Delayed Recall				
Before treatment	3.30 ± 0.98	3.80 ± 0.88	4.10 ± 0.88	3.73 ± 0.96
After treatment	4.53 ± 0.73	4.50 ± 0.73	4.57 ± 0.56	4.53 ± 0.67
Test*	p < 0.001	p < 0.001	p = 0.001	p < 0.001
Attention, Concentration, Memory				
Before treatment	3.33 ± 1.18	3.63 ± 1.42	3.63 ± 1.27	3.53 ± 1.29
After treatment	3.60 ± 1.22	3.93 ± 1.33	3.83 ± 1.23	3.79 ± 1.25
Test*	p = 0.05	p = 0.02	p = 0.11	p = 0.001
Total MoCA				
Before treatment	22.50 ± 1.13	23.90 ± 1.56	24.40 ± 1.83	23.60 ± 1.72
After treatment	25.10 ± 1.47	25.53 ± 1.52	26.00 ± 1.62	25.56 ± 1.55
Test*	p < 0.001	p < 0.001	p < 0.001	p < 0.001

*Paired T test, ¥: Because the standard deviation being zero, was not analyzed; statistical significance p < 0.05; MoCA = Montreal Cognitive Assessment.

Table 4. Significance levels between groups of total MOCA score before treatment and after treatment.

MoCA total score	MoCA before treatment			MoCA after treatment		
	Group1	Group 2	Group 3	Group1	Group 2	Group 3
Before treatment						
Group 1	-	0.002*	< 0.001*			
Group 2	0.002*	-	0.42			
After treatment						
Group 1				-	0.51	0.05
Group 2				0.51	-	0.41

*Statistical significance p < 0.05.

A meta-analysis that included 7,688 participants showed an increased risk of cognitive impairment in those with low vitamin D levels compared to those with normal vitamin D levels (odds ratio 2.39, 95% confidence interval 1.91–3.00; $p < 0.000$)¹⁹.

Studies that have assessed subgroups have generally been conducted on groups of individuals of an older age. A study conducted by Miller et al.²⁰ found that ethnically-different older adults exhibiting a high prevalence of vitamin D insufficiency or deficiency were associated with a decline in cognitive function domains. Four cognitive domains (episodic memory, semantic memory, visual perception, and executive function) were measured. The cognitive decline rate associated with hypovitaminosis D (insufficiency and deficiency) was strongly associated with Alzheimer's dementia for episodic memory and executive function. In our study, we found a more significant difference in language and delayed memory.

McGrath et al.¹² divided participants into three groups of adolescents (12–17 years), adults (20–60 years), and an older group (60–90 years) to investigate the correlation between vitamin D levels and cognitive performance. They did not find a correlation between 25(OH)D levels and cognitive function in the adolescent or adult groups. They found that vitamin D did not affect cognitive function in the adult age group. In our study, the MoCA scores of all participants were within the normal limits in accordance with the literature. However, there was a significant difference in the MoCA scores after treatment.

A systematic review conducted by Annweiler et al.²¹ showed that vitamin D deficiency may negatively affect specific cognitive functions, such as episodic memory, which have not been fully investigated. Studies that have evaluated total cognitive performance (Clinical Dementia Rating or Mini Mental State Examination) have reported a significant correlation with a vitamin D deficiency.

In conclusion, the significant positive correlation between serum 25(OH)D concentrations and cognitive function is controversial when considering age^{5,7,12,13,22}. Recent evidence has shown that vitamin D may reduce age-related tau hyperphosphorylation, nitrosative protein damage²³, formation of A β oligomers. It has been shown that the active 25(OH)D metabolites rebalance inflammation and promote A β phagocytosis in mononuclear cells of peripheral blood in patients with Alzheimer's disease^{24,25}. Despite the limited number of studies, the more intense distribution of the vitamin D receptor in some regions of the brain suggests that 25(OH)D may affect certain neurotransmitters and cortical

functions. Expression of the vitamin D receptor has been identified in the hippocampus and prefrontal cortex areas. These areas are important for learning, memory, and executive control^{12,25,26,27,28,29}. *In vitro* and animal studies have shown that low 25(OH)D increased white matter hyperintensities^{30,31} and ventricular volumes^{32,33}. The results of these studies suggest that a low 25(OH)D level alters development of the brain.

Several issues must be considered when evaluating this process. These issues are: 1) whether the pathophysiology of this process is relevant for chronic period or; 2) it occurs if a person is exposed to vitamin D deficiency but for how long time and at what level; 3) whether a decrease in cognitive functions seen at early ages are caused by the same mechanism; iv) whether genetic factors, especially vitamin D receptor gene polymorphisms affect this process. None of these issues are clearly known.

Some limitations of our study should be discussed. The sample size was small, and all of the participants were female. The educational levels of the participants differed. Cognitive function was assessed by the MoCA but other neuropsychiatric tests could have been performed in conjunction with this test. The MoCA is useful for detecting mild cognitive impairment in older ages, but it is unknown whether it is applicable to younger ages. A brief summary of the verbal and delayed recall in the test analyses (subgroups) may not have provided a precise measure of cognitive function. The test was repeated after three months, so the follow-up time was short.

CONCLUSION

The effect of 25(OH)D on cognitive function is not fully known in the young-adult population. No correlation was found between the vitamin D level and cognitive function in young adults compared with older ages in the small number of studies in the literature. However, the subgroups have not been adequately investigated. The 25(OH)D levels of the patients participating in our study were low and, when evaluated with the MoCA before and after vitamin D replacement, there was a significant difference in the MoCA total scores before treatment and after treatment, especially in the language and delayed recall subgroups. It was difficult to determine how much of this improvement depended on the increase in vitamin D concentration. Prospective, controlled studies with a long-term follow-up are necessary in young adults, including both male and female populations, to reach a definite conclusion.

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