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Association of vitamin D deficiency with cognitive impairment in older women

Cross-sectional study

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ABSTRACT

Objective: The association between low serum 25-hydroxyvitamin D [25(OH)D] concentration and cognitive decline has been investigated by only a few studies, with mixed results. The objective of this cross-sectional population-based study was to examine the association between serum 25(OH)D deficiency and cognitive impairment while taking confounders into account.

Methods: The subjects, 752 women aged ≥75 years from the Epidémiologie de l'Ostéoporose (EPIDOS) cohort, were divided into 2 groups according to serum 25(OH)D concentrations (either deficient, <10 ng/mL, or nondeficient, ≥10 ng/mL). Cognitive impairment was defined as a Pfeiffer Short Portable Mental State Questionnaire (SPMSQ) score <8. Age, body mass index, number of chronic diseases, hypertension, depression, use of psychoactive drugs, education level, regular physical activity, and serum intact parathyroid hormone and calcium were used as potential confounders.

Results: Compared with women with serum 25(OH)D concentrations ≥10 ng/mL (n = 623), the women with 25(OH)D deficiency (n = 129) had a lower mean SPMSQ score ($p < 0.001$) and more often had an SPMSQ score <8 ($p = 0.006$). There was no significant linear association between serum 25(OH)D concentration and SPMSQ score ($\beta = -0.003$, 95% confidence interval −0.012 to 0.006, $p = 0.512$). However, serum 25(OH)D deficiency was associated with cognitive impairment (crude odds ratio [OR] = 2.08 with $p = 0.007$; adjusted OR = 1.99 with $p = 0.017$ for full model; and adjusted OR = 2.03 with $p = 0.012$ for stepwise backward model).

Conclusions: 25-Hydroxyvitamin D deficiency was associated with cognitive impairment in this cohort of community-dwelling older women. ***Neurology*® 2009;73:1–1**

GLOSSARY

25(OH)D = 25-hydroxyvitamin D; **AD** = Alzheimer disease; **BMI** = body mass index; **CI** = confidence interval; **EPIDOS** = Epidémiologie de l'Ostéoporose; **iPTH** = intact parathyroid hormone; **OR** = odds ratio; **SPMSQ** = Short Portable Mental State Questionnaire; **VDR** = vitamin D receptor.

Vitamin D is a secosteroid hormone with multiple biologic targets mediated by the vitamin D receptor (VDR), which is present on many cells,[1,2] including neurons and glial cells. Specific effects of vitamin D on the CNS have been described, such as the regulation of neurotransmission, neuroprotection, and neuroimmunomodulation.[1,2] Furthermore, a reduction in VDR expression in different layers of the hippocampus in patients with Alzheimer disease (AD) has been reported.[3]

Individual vitamin D status is evaluated by measuring the serum concentration of 25-hydroxyvitamin D [25(OH)D]. To date, few studies have explored the association between the serum 25(OH)D concentrations and cognitive status. The reported results were mixed; some showed that low 25(OH)D concentrations were associated with low cognitive performance, whereas others did not.[4-9] Discrepancies may be explained in part by confounding variables that

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were not included in those study analyses, as well as different threshold values used to define vitamin D deficiency. For example, although age, education level, and level of physical activity have been used as confounders in some studies,[6,8,9] the effects of serum intact parathyroid hormone (iPTH) and calcium concentrations, which may influence cognitive performance,[5,10,11] have not yet been taken into account. In addition, the threshold values used to define vitamin D deficiency may vary from 8.4 to 22 ng/mL in community-dwelling elderly populations in Europe.[12] Because clinical adverse health consequences of low serum vitamin D concentrations have been shown for lowest used threshold values of vitamin D deficiency, it has been suggested that 25(OH)D concentrations below 10 ng/mL may indicate a clinically relevant vitamin D deficiency.[12-15]

Based on mentioned study results, we hypothesized that vitamin D deficiency could be associated with cognitive decline in older women. The aim of this study was to examine the association between serum 25(OH)D deficiency (i.e., <10 ng/mL) and cognitive impairment (i.e., Pfeiffer Short Portable Mental State Questionnaire [SPMSQ] score <8) while taking the effects of potential confounders into account in women aged 75 years and older using data from the baseline assessment of the Epidémiologie de l'Ostéoporose (EPIDOS) study.

METHODS

Participants. We studied 752 subjects, a randomized subset of the EPIDOS study, a French large observational prospective multicenter cohort study designed to evaluate risk factors for hip fractures among community-dwelling women aged 75 years and older. The sampling and data collection procedures have been described elsewhere in detail.[16] In summary, from 1992 to 1994, 7,598 subjects chosen from electoral lists were recruited in 5 French cities (Amiens, Lyon, Montpellier, Paris, and Toulouse). Exclusion criteria were the inability to walk independently, a hip fracture or bilateral hip replacement, and the inability to understand or answer the study questionnaires.

Serum measurements. Fasting early morning venous blood was collected from resting subjects for the measurement of serum 25(OH)D. Sera were stored at −100°C until analyses were performed. Serum 25(OH)D concentrations were measured by radioimmunoassay (Incstar Corp., Stillwater, MN). With this method, there is no lipid interference, which is often observed in other nonchromatographic assays of 25(OH)D. The intra-assay and interassay precisions were 5.2% and 11.3%, respectively (range 30–125 nmol/L in normal adults aged 20–60 years). Vitamin D deficiency was strictly defined for 25(OH)D concentrations lower than 10 ng/mL.[12-14]

iPTH was measured by immunochemoluminometric assay (Magic Lite, Ciba Corning Diagnostic, Medfield, MA; normal range for adults aged 20–60 years, 11–55 pg/mL). The intra-assay and interassay precisions were 5.2% to 6.8% and 5.0% to 5.5%, respectively. Serum concentrations of calcium and albumin were measured using automated standard laboratory methods. Because of the high prevalence of hypoalbuminemia in older adults, the corrected calcium value, calculated with serum concentrations of albumin and calcium (corrected calcium value = Ca + 0.02 [46-albumin]), was used in the subsequent analysis. All measurements were performed locally at the University Hospital at Lyon, France.

Assessment of cognitive function. Global cognitive function was assessed using SPMSQ,[17] which is a reliable, standardized, validated screening test for organic brain syndromes. The SPMSQ proved to be a sensitive and specific screening test for moderate to severe dementia for both community dwellers and hospital inpatients.[17,18] It consists of a 10-item questionnaire with a score ranging from 0 to 10. The validated cutoff value for normal functioning is a score of 8 or above.[17,18] In this study, cognitive impairment was defined as an SPMSQ score less than 8.

Confounders. All included study participants received a full medical examination by trained nurses in each local clinical center, which consisted of structured questionnaires, a clinical examination, and anthropometric measurements (i.e., height and weight to calculate the body mass index [BMI] = height/weight^2, kg/m^2). Evaluation of comorbidities was based on self-report. In particular, information about hypertension and depression were obtained from the standardized question: Do you currently suffer from hypertension or depression? Furthermore, the use of psychoactive drugs (benzodiazepines, antidepressants, or neuroleptics) was recorded during baseline assessment. Women were also asked whether they walked outdoors daily and whether they participated in a sport or physical leisure activity regularly (i.e., at least 1 hour a week for at least the past month). In addition, the education level was self-reported with a structured questionnaire. Women who obtained at least the Elementary School Recognition Certificate were considered to have a high level of education compared with those who had not obtained it.

The following confounders were included in the data analysis: age at baseline evaluation, BMI, regular practice of physical activity, number of chronic diseases, hypertension, current depression, use of psychoactive drugs, high level of education, and serum iPTH and calcium concentrations.

Statistical analysis. The subjects' characteristics were summarized using means and standard deviations or frequencies and percentages, as appropriate. The normality of the variables' distribution was verified with skewness and kurtosis tests before and after applying usual transformations to normalize nongaussian variables. First, comparisons between subject groups were performed using the χ^2 test, the independent-samples t test, the Kruskal-Wallis test, or 1-way analysis of variance, as appropriate. Second, a linear regression to predict SPMSQ score from serum 25(OH)D concentration was performed along with a residuals-vs-predictor plot. Residuals were the difference between the observed and predicted values. Third, univariate and multivariate (i.e., full adjusted model and stepwise backward method) logistic regressions were used to examine the association between serum 25(OH)D deficiency (independent variable) and cognitive im-

pairment (dependant variable) while taking the confounders into account. p Values less than 0.05 were considered significant. All statistics were performed using Stata statistical software, version 10.1 (StataCorp LP, College Station, TX).

Standard protocol approvals, registrations, and patient consents. Women participating in the study were included after having given their written informed consent for research. The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki (1983). The project was approved by the local ethics committee of each city.

RESULTS One hundred twenty-nine women (17.2%) had a vitamin D deficiency defined as a serum 25(OH)D concentration <10 ng/mL. Their mean 25(OH)D concentration was 7.21 ± 2.09 ng/mL. As indicated in table 1, the 25(OH)D-deficient women had lower mean SPMSQ scores ($p < 0.001$), and the prevalence of SPMSQ score below 8 was higher compared with women with serum 25(OH)D concentrations ≥10 ng/mL ($p = 0.006$) (table 1). There were no significant differences for the other clinical characteristics. In addition, serum iPTH concentration was higher among women with 25(OH)D deficiency compared with women with serum 25(OH)D concentrations ≥10 ng/mL ($p < 0.0001$) (table 1).

There was no significant linear association between serum 25(OH)D concentration and SPMSQ score (slope of the regression $\beta = -0.003$, 95% confidence interval [CI] −0.012 to 0.006, $p = 0.512$). In addition, the residuals vs the serum 25(OH)D concentration found patterns that were not evenly distributed along the range of serum 25(OH)D concentration.

Table 2 shows univariate and multivariate logistic regressions between cognitive impairment defined as an SPMSQ score <8, serum 25(OH)D deficiency, and baseline characteristics, with odds ratio (ORs) and CIs for each crude, adjusted, and stepwise backward model. Serum 25(OH)D deficiency was associated with cognitive impairment (crude OR = 2.08 with $p = 0.007$; adjusted OR = 1.99 with $p = 0.017$ for full regression model), even after adjustment for all confounders (table 2). Moreover, vitamin D deficiency remained associated with cognitive impairment in the stepwise backward regression model (adjusted OR = 2.03 with $p = 0.012$). Furthermore, older age (crude OR = 1.12 with $p = 0.001$; adjusted OR = 1.12 with $p = 0.001$ for full model; and OR = 1.11 with $p = 0.001$ for stepwise backward model) and a high BMI (crude OR = 1.05 with $p = 0.047$; adjusted OR = 1.07 with $p = 0.011$ for full model, and OR = 1.07 with $p = 0.014$ for stepwise backward model) were also associated with cognitive impairment, whereas the high education level was associated with better cognitive performance (crude OR = 0.46 with $p = 0.042$; adjusted OR = 0.45 with $p = 0.042$ for full model; and OR = 0.47 with $p = 0.054$ for stepwise backward model).

Table 1 Characteristics and comparison of the randomized sample subjects (n = 752) separated into 2 groups based on serum 25(OH)D concentrations

	Serum 25(OH)D concentration		
	<10 ng/mL (n = 129)	≥10 ng/mL (n = 623)	p Value*
Clinical measures			
Age, mean ± SD, y	80.7 ± 3.8	80.1 ± 3.4	0.129
Body mass index, mean ± SD, kg/m^2	25.5 ± 4.4	25.8 ± 4.4	0.577
Regular physical activity,† n (%)	61 (47.3)	336 (54.0)	0.459
No. of chronic diseases,‡ mean ± SD	3.1 ± 1.8	3.0 ± 1.8	0.340
Use of psychoactive drugs,§ n (%)	65 (50.4)	290 (46.6)	0.440
Hypertension,‡ n (%)	63 (48.8)	303 (49.0)	1.000
High education level,¶ n (%)	107 (83.6)	498 (80.2)	0.460
Neuropsychological measures			
Pfeiffer SPMSQ score, /10			
Mean ± SD	8.56 ± 1.67	9.05 ± 1.34	<0.001
<8, n (%)	22 (17.1)	56 (9.0)	0.006
Depression,‖ n (%)	14 (10.9)	85 (13.7)	0.475
Serum measures			
25(OH)D concentration, mean ± SD, ng/mL	7.2 ± 2.1	20.1 ± 10.8	<0.001
iPTH concentration, mean ± SD, pg/mL	70.7 ± 35.2	57.7 ± 25.2	<0.001
Calcium concentration,# mean ± SD, mmol/L	2.2 ± 0.1	2.2 ± 0.1	0.695

*Comparisons based on χ^2 test, the independent samples t test, the Kruskal-Wallis test, or 1-way analysis of variance, as appropriate. $p < 0.05$ significant.
†At least 1 hour recreational physical activity (walking, gymnastics, cycling, swimming, or gardening) per week for the past month or more.
‡Obtained from physical examination and a health status questionnaire to target chronic diseases (hypertension, diabetes, dyslipidemia, coronary heart disease, chronic obstructive pulmonary disease, peripheral vascular disease, cancer, stroke, Parkinson disease, and depression).
§Use of benzodiazepines, antidepressants, or neuroleptics.
¶Obtained from a structured questionnaire; high education level considered when Elementary School Recognition Certificate has been passed.
‖Self-reported measure based on the following question: Do you currently suffer from depression?
#Corrected value based on the formula (Ca + 0.02 [46-albumin]).
25(OH)D = 25-hydroxyvitamin D; SPMSQ = Short Portable Mental State Questionnaire; iPTH = intact parathyroid hormone.

DISCUSSION The main finding of our study was that serum 25(OH)D deficiency was significantly associated with cognitive impairment defined as a SPMSQ score below 8, even after adjustment for all potential confounders.

Few studies, with mixed results, are available on the association between serum 25(OH)D concentration and cognitive function.[4-9] Some results highlighted a significant association between serum 25(OH)D concentrations and cognitive performance. Low serum 25(OH)D concentration has

Table 2 Univariate and multivariate logistic regression showing the cross-sectional association between cognitive impairment measured with Pfeiffer SPMSQ score (dependent variable) and serum 25(OH)D deficiency (independent variable) adjusted for subjects' baseline characteristics (n = 752)

	Cognitive impairment*								
	Crude model			Full model			Stepwise backward model		
	OR	95% CI	*p* Value	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Serum 25(OH)D <10 ng/mL	2.08	(1.22–3.55)	0.007	1.99	(1.13–3.52)	0.017	2.03	(1.17–3.53)	0.012
Age	1.12	(1.05–1.19)	0.001	1.12	(1.00–1.19)	0.001	1.11	(1.04–1.19)	0.001
Body mass index	1.05	(1.00–1.11)	0.047	1.07	(1.02–1.13)	0.011	1.07	(1.01–1.13)	0.014
Regular physical activity†	0.96	(0.60–1.54)	0.865	1.34	(0.80–2.25)	0.262	—	—	—
No. of chronic diseases‡	0.94	(0.83–1.08)	0.392	0.92	(0.79–1.07)	0.264	—	—	—
Use of psychoactive drugs§	1.13	(0.71–1.81)	0.602	1.07	(0.64–1.77)	0.802	—	—	—
Hypertension‡	1.11	(0.69–1.78)	0.670	1.05	(0.62–1.78)	0.865	—	—	—
High education level¶	0.46	(0.22–0.97)	0.042	0.45	(0.21–0.97)	0.042	0.47	(0.22–1.01)	0.054
Depression‖	1.11	(0.56–2.18)	0.763	1.52	(0.72–3.20)	0.275	—	—	—
iPTH, pg/mL	1.01	(1.00–1.02)	0.017	1.01	(1.00–1.01)	0.206	—	—	—
Calcium,# mmol/L	0.60	(0.08–4.79)	0.631	0.87	(0.10–7.23)	0.869	—	—	—

$p < 0.05$ significant.
*Measured with Pfeiffer Short Portable Mental State Questionnaire (SPMSQ) and based on cutoff value <8.
†At least 1 hour recreational physical activity (walking, gymnastics, cycling, swimming, or gardening) per week for the past month or more.
‡Obtained from physical examination and a health status questionnaire to target chronic diseases (i.e., hypertension, diabetes, dyslipidemia, coronary heart disease, chronic obstructive pulmonary disease, peripheral vascular disease, cancer, stroke, Parkinson disease, and depression).
§Use of benzodiazepines, antidepressants, or neuroleptics.
¶Obtained from a structured questionnaire; high education level considered when Elementary School Recognition Certificate has been passed.
‖Self-reported measure based on the following question: Do you currently suffer from depression?
#Corrected value based on the formula (Ca + 0.02 [46-albumin]).
25(OH)D = 25-hydroxyvitamin D; OR = odds ratio; CI = confidence interval; iPTH = intact parathyroid hormone.

been associated with low cognitive performance, and high serum 25(OH)D concentration has been associated with high cognitive performance.[6,7,9] In contrast, others studies did not report any significant association.[5,6,8] Mixed findings may in part be due to the choice of tests used to assess cognitive performance. Studies that focused on several subtests exploring specific aspects of cognition, such as executive or learning functions, did not show any association with serum 25(OH)D concentrations.[5,8] In contrast, but similar to our findings, an association of low serum 25(OH)D concentrations with low global cognitive performance assessed by the Hasegawa Dementia Screening Scale,[4] Clinical Dementia Rating,[6] or Mini-Mental State Examination[7,9] has been previously reported.

How to take into account cognitive performance may also explain mixed findings, because one study used cognitive performance as a categorical variable,[8] whereas others used it as a continuous score[5-7,9] without checking for the normality of its distribution.[6-9] In our study, there was no significant linear association between serum 25(OH)D concentration and SPMSQ score, which was confirmed by noneven distribution of the residuals. Nevertheless, this result has to be mitigated because of the lack of data about a dose-dependent relationship between SPMSQ score and severity of cognitive impairment. The only valid way to explore an association of SPMSQ score with 25(OH)D concentration should also use binary SPMSQ score with the validated cutoff value of 8.[17,18] In addition, providing a result in terms of linear association, i.e., showing a change in SPMSQ score related to a variation of 1 ng/mL of serum 25(OH)D, has poor impact for clinical practice compared with showing an association between impaired cognitive performance and vitamin D deficiency.

Besides, different threshold values used to define vitamin D deficiency may also explain previous mixed results. As an example, the only nonsignificant association between low serum 25(OH)D concentration and low global composite cognitive score has been found with a threshold fixed at 20 ng/mL,[6] whereas adverse health consequences have been reported in other studies

only when serum 25(OH)D concentrations were chronically below 10 ng/mL.[12-14] For example, low serum 25(OH)D concentration and low bone mineral density of the hip were associated at concentrations below 10 ng/mL but not at higher serum 25(OH)D concentrations.[13] There is also evidence of a higher incidence of rickets and osteomalacia with 25(OH)D concentrations below 10 ng/mL compared with higher 25(OH)D concentrations.[14]

Last, mixed results on the association between serum 25(OH)D concentration and cognitive performance may in part result from the absence or incomplete inclusion of potential confounders. Although age, BMI, and education level—which were also related to cognitive performance in our study—have been used as potential confounders in previous studies,[6,8,9] the effect of serum iPTH and calcium concentrations, which are both related to vitamin D and cognition,[5,10,11] had never been taken into account. Several studies reported the involvement of increased intracellular calcium in neuronal cell death[11] and showed that high serum calcium concentrations were associated with faster decline in cognitive function over age 75 years.[10] No association between increased calcium and decreased cognitive performance was shown in our study, most likely because the serum calcium concentrations were normal in both groups of subjects. Furthermore, high serum iPTH levels have been significantly associated with poor performance in several specific cognitive tasks,[5] and it has been reported that the clinical features of hyperparathyroidism include dementia,[19] which could be reversed after parathyroidectomy.[19] Our results were in accord with this statement because a high serum iPTH concentration was significantly associated with cognitive impairment in the sample of studied women. It is therefore necessary to adjust on the effects of both serum calcium and iPTH when exploring the association between serum 25(OH)D concentration and cognitive performance.

Exactly how vitamin D and cognition are associated and whether this association is causal remain unclear. On one hand, low cognitive function could lead to low dietary intake of vitamin D or a lack of sunlight exposure, which in turn could lead to low vitamin D serum concentrations.[12] However, this first hypothesis needs to be mitigated by the fact that the studied population of the EPIDOS study was relatively healthy, with high BMI and regular practice of physical activity, without any significant differences between the women who were deficient in vitamin D and those who were not, and because the association between serum 25(OH)D deficiency and cognitive impairment remained significant even after adjustment for these covariables. A scenario of reverse causation is plausible and should be considered. Evidence precisely supports a role for vitamin D in the CNS.[1,2,20] Animal experiments have shown that vitamin D has neurotrophic, neuroprotective, and immunomodulating properties and is involved in neurotransmitter metabolism and the synthesis of certain growth factors, such as glial cell line–derived neurotrophic factor.[1,2,20] Furthermore, it has been shown that VDR-knockout transgenic mice had uncoordinated lower-limb movements resulting in a decreased swimming capacity.[21] In humans, a significant reduction in the number of cerebral VDR has been reported in AD.[3] In addition, the VDR gene polymorphism, which decreases the affinity of the VDR for vitamin D, could affect the mechanisms of neuroprotection, detoxification, regulation of neurotrophic factors, and calcium homeostasis and could also be involved in neuronal aging and damages in neurodegenerative diseases.[22] For example, 3 markers on chromosome 12, which contains the VDR gene, are associated with late-onset AD.[23] Furthermore, a significant association between AD and the ApaI polymorphism was shown among 104 patients with AD and 109 aged-matched controls, with the presence of the Aa genotype associated with a 2.3-fold higher risk of developing AD compared with the AA genotype.[22]

Our study has some limitations. First, the study cohort was restricted to women and included relatively healthy, vigorous subjects. Therefore, the studied sample may not be representative of community-dwelling older adults in general. Moreover, the study participants may be more motivated with a greater interest in personal health issues than the general population of older adults in independent senior living facilities. Second, the cross-sectional design of the present study may limit the exploration of the relationship between serum 25(OH)D concentrations and cognitive status and does not allow any causal inference compared with prospective longitudinal cohort studies. Third, the SPMSQ is a crude measure of global cognitive function, and fluctuations in cognition could have been missed.[9,17,18] Fourth, although we were able to control for many characteristics likely to modify this relationship, residual potential confounders may still be present.

This study reports an association between low serum 25(OH)D concentrations and cognitive impairment in older women. Future analyses are needed to confirm these results and to further clarify the effects of vitamin D on cognitive functions using specifically designed tasks to measure neuropsychological functions such as memory, executive function, and/or attention, known to be linked to a particular

brain structure or pathway and to be sensitive to the effect of age. Additional knowledge in this field may allow simple interventions, such as substituting vitamin D, to provide subjectively and clinically important changes such as improving or maintaining cognitive function.

AUTHOR CONTRIBUTIONS

Statistical expertise: F.R. Herrmann, MD, MPH (Department of Rehabilitation and Geriatrics, Geneva University Hospitals and University of Geneva, Switzerland).

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DISCLOSURE

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