The present study shows that serum FGF21 levels are independently associated with renal function and CKD in community-dwelling adults. These findings are consistent with two previous studies that suggested that circulating FGF21 concentrations were associated with renal function in individuals with diabetes mellitus and in a mixed population of healthy controls and patients undergoing hemodialysis or with CKD. In the present study, the relationship between serum FGF21 and renal function and CKD was consistent even after exclusion of participants with diabetes mellitus.

Serum FGF21 concentrations may be higher in individuals with poorer renal function because of inability of the kidneys to clear FGF21 in the urine. An alternative explanation may be that high FGF21 is causally related to poorer renal function, but currently there is little evidence to support such a hypothesis. In any case, the findings from the present study highlight the potential importance of adjusting for renal function in future epidemiological studies of circulating FGF21.

The strengths of this study include the large sample size of community-dwelling adults and the rigorously timed and standardized collection of fasting serum samples, because FGF21 levels have been shown to have a circadian rhythm. A limitation of the study is the cross-sectional design, because the direction of the association between high circulating FGF21 and renal function is unknown. Further studies are needed to determine whether high levels of circulating FGF21 precede compromised renal function or serve as a biomarker that is retained as renal function declines.

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4. Lin Z, Wu Z, Yin X et al. Serum levels of FGF-21 are increased in coronary heart disease patients and are independently associated with adverse lipid profile. PLoS ONE 2010;5:e15534.

COGNITIVE EFFECTS OF VITAMIN D SUPPLEMENTATION IN OLDER OUTPATIENTS VISITING A MEMORY CLINIC: A PRE–POST STUDY

To the Editor: Vitamin D is a neurosteroid hormone that may be involved in cognition in older adults.1–3 Supporting epidemiological evidence is primarily based on cross-sectional studies, and the lack of placebo-controlled intervention studies prevents inferring a causal relationship.4 In particular, the single pre–post study on this topic found no effect of vitamin D2 supplementation on cognition in institutionalized older adults.5 However, the use of vitamin D2 supplements, which are less effective than D3 for replacement,6 a 4-week follow-up, which might have been too short to capture any treatment effects; and the failure to assess executive functions, even if these domain-specific cognitive functions seem related to vitamin D status,7,8 limited that study. The objective of the current study was to examine in a pre–post design the medium-term effects of vitamin D3 supplementation on cognition, in particular on executive functions, in elderly outpatients visiting a memory clinic.

All outpatients with no recent vitamin D supplementation and no prescription of antidementia drugs (anticholinesterase or memantine) who visited the University Memory Centre of Angers, France, twice between June 2009 and October 2011 and gave informed consent for research were enrolled in this retrospective pre–post cohort study. The prescription of oral vitamin D3 during the first visit was excluded from the analysis to prevent contamination. An objective reason, such as the hospital prescription records (800 IU/d or 100,000 IU/month), except for patients who were autonomous, a nurse dispensed D3 supplements to ensure adherence to treatment. Global cognitive function was assessed at baseline and follow-up visits using the Mini-Mental State Examination (MMSE, total score of 30) and the Cognitive
Assessment Battery (CAB, total score of 96), and executive functions were assessed using the Frontal Assessment Battery (FAB, total score of 18). The score change on each cognitive test was calculated from the formula: score after treatment – score before treatment. Some of the patients had serum 25-hydroxyvitamin D (25OHD) levels measured at baseline and follow-up visits (Table 1). Multiple regression models were performed to examine associations between use of vitamin D3 supplements and change on each cognitive score. Age, sex, cognitive score at baseline and between-visit time were used as covariates. P < .05 was considered statistically significant. All analyses were performed using SPSS, version 19.0, (SPSS, Inc., Chicago, IL). The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki (1983). The local ethical committee of Angers approved the entire study protocol.

Of 44 outpatients included (median age 80.6, interquartile range 14.0; 54.5% female; 100% Caucasian), 20 received vitamin D3 supplements. There was no difference between the vitamin D3 and control groups at baseline, especially regarding cognitive scores and serum 25OHD concentration (Table 1). After 16 months of follow-up, the vitamin D3 group had higher 25OHD concentrations than at baseline (P = .001) and higher than those of the control group (P < .001). The vitamin D3 group had also higher final scores on the MMSE, CAB, and FAB than the control group and greater score changes on each cognitive test (Table 1). In particular, in the vitamin D3 group, an improvement of FAB score accompanied the increase in 25OHD concentration (P = .02). Vitamin D supplementation was associated with score change on the MMSE (adjusted β = 2.23, 95% confidence interval (CI) = 0.38–4.07, P = .02), the CAB (adjusted β = 5.55, 95% CI = 0.64–10.47, P = .03), and the FAB (adjusted β = 1.85, 95% CI = 0.30–3.39, P = .02). Vitamin D supplementation was also associated with improvement in MMSE (odds ratio (OR) = 3.80, 95% CI = 1.02–14.21, P = .047), CAB (OR = 16.50, 95% CI = 2.51–108.60, P = .004), and FAB (OR = 8.00, 95% CI = 1.52–42.04, P = .01) scores.

The use of vitamin D3 supplements, irrespective of potential confounders, was associated with medium-term improvement in cognitive performance in older adults and in particular with better executive functioning. The present pre–post study used vitamin D3 supplements over a longer period than a previous study, which may explain why a treatment effect was captured. Additionally, the control group in the previous study may have received vitamin D routinely during follow-up (mean 25OHD stable at approximately 34 ng/mL), whereas the control group in

Table 1. Characteristics and Comparison of Subjects (N = 44) Based on the Use of Vitamin D3 Supplements

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Cohort (N = 44)</th>
<th>Vitamin D3 Group (n = 20)</th>
<th>Control Group (n = 24)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>80.6 (14.0)</td>
<td>81.9 (13.2)</td>
<td>75.9 (15.0)</td>
<td>.78</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>24 (54.5)</td>
<td>11 (55.0)</td>
<td>13 (54.2)</td>
<td>.96</td>
</tr>
<tr>
<td>Body mass index, kg/m², median (IQR)</td>
<td>25.2 (3.0)</td>
<td>25.6 (2.0)</td>
<td>24.7 (4.0)</td>
<td>.32</td>
</tr>
<tr>
<td>Diagnosis of Alzheimer’s disease, n (%)</td>
<td>10 (22.7)</td>
<td>3 (15.0)</td>
<td>7 (29.2)</td>
<td>.26</td>
</tr>
<tr>
<td>Number of comorbidities, median (IQR)</td>
<td>3.0 (3.0)</td>
<td>3.0 (3.0)</td>
<td>3.0 (3.0)</td>
<td>.81</td>
</tr>
<tr>
<td>High school education or more, n (%)</td>
<td>19 (43.2)</td>
<td>9 (45.0)</td>
<td>10 (41.7)</td>
<td>.82</td>
</tr>
<tr>
<td>Use of psychoactive drugs, n (%)</td>
<td>5 (11.4)</td>
<td>2 (20.0)</td>
<td>3 (17.6)</td>
<td>.88</td>
</tr>
<tr>
<td>Time between visits, months, median (IQR)</td>
<td>15.7 (7.8)</td>
<td>16.6 (7.5)</td>
<td>15.4 (10.3)</td>
<td>.44</td>
</tr>
<tr>
<td><strong>Neuropsychological measures, median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-Mental State Examination score (/30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>27.0 (4.0)</td>
<td>27.0 (4.0)</td>
<td>27.0 (4.0)</td>
<td>.63</td>
</tr>
<tr>
<td>After treatment</td>
<td>26.5 (5.0)</td>
<td>28.0 (4.0)</td>
<td>24.0 (4.0)</td>
<td>.04</td>
</tr>
<tr>
<td>Between-visit change</td>
<td>0.0 (3.0)</td>
<td>1.0 (1.0)</td>
<td>−2.0 (4.0)</td>
<td>.01</td>
</tr>
<tr>
<td>Cognitive Assessment Battery score (/96)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>88.0 (9.0)</td>
<td>88.0 (10.0)</td>
<td>88.0 (12.0)</td>
<td>.41</td>
</tr>
<tr>
<td>After treatment</td>
<td>89.0 (10.0)</td>
<td>90 (12.0)</td>
<td>89.00 (6.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Between-visit change</td>
<td>1.0 (6.3)</td>
<td>2.0 (4.0)</td>
<td>0.0 (6.0)</td>
<td>.02</td>
</tr>
<tr>
<td>Frontal Assessment Battery score (/18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>15.5 (4.0)</td>
<td>15.0 (5.0)</td>
<td>16.0 (3.0)</td>
<td>.83</td>
</tr>
<tr>
<td>After treatment</td>
<td>16.0 (2.0)</td>
<td>16.0 (2.0)</td>
<td>15.0 (3.0)</td>
<td>.04</td>
</tr>
<tr>
<td>Between-visit change</td>
<td>0.0 (3.0)</td>
<td>1.0 (2.0)</td>
<td>−1.0 (1.0)</td>
<td>.01</td>
</tr>
<tr>
<td>Serum 25-hydroxyvitamin D concentration, nmol/L, median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>54.0 (12.2)</td>
<td>42.0 (23.0)</td>
<td>63.0 (5.0)</td>
<td>.08</td>
</tr>
<tr>
<td>After treatment</td>
<td>65.5 (36.0)</td>
<td>75.0 (24.0)</td>
<td>48.0 (19.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Between-visit change</td>
<td>12 (56.5)</td>
<td>30.0 (47.0)</td>
<td>−17.0 (27.0)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Comparisons between vitamin D3 group and control group based on chi-square test or Mann Whitney U-test, as appropriate.
1Diseases lasting at least 3 months or running a course with minimal change.
2Benzodiazepines, antidepressants, or neuroleptics.
3Calculated from the formula: score after treatment – score before treatment.
4Based on 27 blood collections at the baseline visit (14 in the vitamin D3 group and 13 in the control group, P = .28).
5Based on 41 blood collections at the follow-up visit (19 in the vitamin D3 group and 22 in the control group, P = .66).
6IQR = interquartile range.
the current study was not taking any vitamin D supplements, as illustrated by the decrease in 25OHD concentration during follow-up (Table 1). With this design, the effect of receiving vs not receiving vitamin D supplements and, indirectly, the effect of increasing vs decreasing 25OHD concentrations was captured. Finally, an improvement was also found in executive functions after vitamin D3 supplementation. This is concordant with previous studies suggesting that brain structures underlying executive functions are the target of neuroprotective and vasculoprotective properties of vitamin D.\(^1,3,7,8\) Nevertheless, the pre-post design of the current study without randomization limits the exploration of the cognitive effect of vitamin D repletion. Placebo-controlled randomized clinical trials are needed to corroborate these results with higher levels of evidence.

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Author Contributions: Annweiler had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. Annweiler and Beauchet: Study concept and design. Annweiler, Beauchet, and Gautier: Acquisition of data. Annweiler, Fantino, and Beauchet: Analysis and interpretation of data. Annweiler and Beauchet: Drafting of the manuscript. Fantino, Gautier, Beaudenon, and Thiery: Critical revision of the manuscript for important intellectual content. Annweiler: Statistical expertise. Annweiler and Beauchet: Administrative, technical, or material support. Beauchet: Study supervision.

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OUTCOME OF SURGICAL TREATMENT FOR COMPLICATED HUMERAL SHAFT FRACTURES IN ELDERLY ADULTS WITH OSTEOPOROSIS

To the Editor: Although the majority of humeral shaft fractures sustained by elderly adults with osteoporosis can be successfully managed nonoperatively,\(^1–3\) at the First Orthopedic Clinic, Medical School, Aristotle University of Thessaloniki, “G. Papanikolaou” Hospital (Thessaloniki, Greece), excellent results have been achieved with the selection of surgical treatment for different types of humeral shaft fractures in a cohort of such individuals.

Over a 27-year period (1984–2011), 182 elderly adults with osteoporosis (mean age 66.5, range 57–87; 142 female (mean T-score 3.89), 40 male (mean T-score 3.13); 190 humeral shaft fractures; classification according to Arbeitsgemeinschaft für Osteosynthesefragen Association for the Study of Internal Fixation: AO 12 were treated using internal fixation.

Fracture classification was performed according to AO principles.\(^4\) The indications were 73 patients with multiple fractures, 51 fractures with coexisting primary radial nerve injury, 12 Goustillo Grade I or II, eight bilateral and 50 insufficient reductions after conservative treatment; 115 fractures were located at the middle third, 32 at the upper third, and 43 at the lower third of the humeral bone; 73 were comminuted (AO 12 C and AO 12 B), 95 transverse (AO 12 A3), eight oblique (AO 12 A2) and 15 spiral (AO 12 A1).

A standard anterolateral approach (Thompson and Henry) was performed, and the radial nerve was routinely identified and exposed. Fracture stabilization was mainly performed using a 4-mm self-compressing dynamic compression plate (DCP) (114 cases) and a low-contact (LC) DCP (76 cases) with 4.5-mm cortical screws. In 54 of these cases, compression lag screws were applied. A Y-shaped DCP plate was used in eight cases. Autologous iliac crest grafts were used in 30 cases because of the lack of medial cortex integrity. The addition of cement in these cases, compression lag screws were applied. A Y-shaped DCP plate was used in eight cases. Autologous iliac crest grafts were used in 30 cases because of the lack of medial cortex integrity. The addition of cement in these cases, compression lag screws were applied. A Y-shaped DCP plate was used in eight cases. Autologous iliac crest grafts were used in 30 cases because of the lack of medial cortex integrity.