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PARATHYROID HORMONE, VITAMIN D, AND COGNITIVE DECLINE IN OLDER PEOPLE WITH A HISTORY OF VASCULAR DISEASES

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Abstract: *Introduction:* Cross-sectional and prospective follow-up studies have suggested serum 25-hydroxyvitamin D (25-OHD) to associate with cognitive decline. However, other regulators of calcium homeostasis, such as parathyroid hormone (PTH), may confound this association. In this prospective three-year follow-up study the predictive value of both 25-OHD and PTH for cognitive decline were investigated. *Methods:* Older community-dwelling people (N=400, age=80±5 years) with a history of vascular diseases were included. In addition to thorough clinical examination cognition was assessed by Consortium to Establish a Registry for Alzheimer Disease neuropsychological assessment battery total score (CERAD) at baseline and after three-year follow-up. Baseline serum 25-OHD, PTH, total calcium, creatinine and apolipoprotein E4 genotype were determined. *Results:* The mean baseline MMSE score was 26±3 and that of total CERAD score 69±12. A weak inverse association was observed between baseline PTH levels and CERAD total scores (r= -0.120, p=0.023). The highest baseline PTH quartile (≥83.1 ng/l) compared with lower quartiles was associated with 2.4-fold risk (95%CIs=1.05-5.35) for at least 10-point decline in CERAD total score within three years. The risk remained significant after controlling for age, gender, education, apolipoprotein E4, baseline CERAD score, body mass index, creatinine, total calcium, and 25-hydrovitamin D. No significant associations were found between baseline 25-OHD and cognition in cross-sectional or longitudinal analyses. *Conclusion:* High baseline levels of PTH are associated independently of baseline vitamin D status with clinically significant cognitive decline in older community-dwelling people with a history of vascular diseases. Further studies are warranted to address the role of PTH and its regulators in the etiology of cognitive impairment.

Key words: Cognitive decline, parathyroid hormone, vitamin D, aging, vascular diseases.

Introduction

Vitamin D deficiency, common in older people, has been associated with various chronic diseases, eg. cancer, cardiovascular diseases, autoimmune diseases, diabetes, obesity, and osteoporosis (1). Animal studies and cell models have suggested that vitamin D may have neuroprotective effects (2). Low levels of 25-OHD have been related to impaired cognition in some cross-sectional studies (3), but the association has not been consistent (4). Furthermore, most studies on association between 25-OHD and cognitive function lack data on parathyroid hormone (PTH) that together with 25-OHD is an important regulator of calcium homeostasis. Interestingly, some small cross-sectional studies have associated high PTH levels with impaired cognition (5, 6).

Prospective follow-up studies have shown that vitamin D deficiency is associated with cognitive decline in an Italian population based sample of older persons and in older Caucasian women enrolled in an osteoporosis study (7, 8). Furthermore, vitamin D deficiency has been shown to predict the onset of non-Alzheimer dementias among older French women (9). Again, all these studies lacked data on PTH levels. Furthermore, the results of the follow-up studies have not been consistent (10). In our previous prospective follow-up study we have shown that high PTH levels are associated with significant cognitive decline in a general aged population (11). However, this study lacked in turn data on vitamin D levels.

The assessment of cognition has been based on screening methods, such as the Mini Mental State Examination, in many of the previous studies, even though the role of the Consortium to Establish a Registry

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for Alzheimer Disease (CERAD) neuropsychological assessment battery has been emphasized in the detection of cognitive changes over time (12, 13). Furthermore, in contrast to the plethora of vitamin D supplementation trials, some small parathyroidectomy studies have reported minor improvements in cognitive functions (14-16), suggesting even causality between PTH levels and cognition.

According to our hypothesis elevation of PTH levels predicts cognitive decline independently of vitamin D status. In order to compare the predictive value of baseline measurements of these variables both 25-OHD and PTH levels were related to cognitive decline assessed by CERAD within three-year follow-up in older people with a history of vascular diseases.

Methods

The Drugs and Evidence Based Medicine in the Elderly (DEBATE) Study database was used for these analyses. The trial design including the randomization procedure and the flow chart of the DEBATE study have been published in detail previously (17). Briefly, in a population-based setting, a total of 400 home-dwelling older patients were recruited into a three-year multifactorial, controlled secondary prevention trial. Pre-study postal questionnaires were sent to a random sample of 75 to 95-year-old individuals (n=4821) living in Helsinki, Finland. During the first visit, the atherosclerotic disease (prior myocardial infarction, coronary artery disease, previous stroke or transient ischaemic attack, peripheral artery disease) was confirmed (82% coronary heart disease), the patients signed an informed consent, where after they were randomized to the intervention (n=199) and control groups (n=201) of the multifactorial prevention study. In the intervention group, treatments were tailored according to 1998 European guidelines by a geriatrician-internist with consultations as appropriate. The control group received usual care by primary care physicians, and visited only the study nurse (not the study geriatrician) yearly.

The research protocol of the DEBATE study was approved by the Ethics Committee of the Department of Medicine, University of Helsinki. The intervention did not have an effect on the primary endpoints and the study has been continued as a follow-up study. The main results of the trial have been published elsewhere (18).

Cognition was assessed by Consortium to Establish a Registry for Alzheimer Disease neuropsychological assessment battery total score (CERAD, range 0-100 points) (12), by Mini Mental State Examination (MMSE, range 0-30 points) (19), and by Clinical Dementia Rating total score (CDR, 0 = none, 0.5 = very mild, 1 = mild, 2 = moderate, and 3 = severe) (20) at baseline and at three-year re-examination. The clinically meaningful decline for CERAD total score was at least 10 points (13), the respective figure was at least 4 points for MMSE. Any worsening in total CDR score was considered meaningful.

Venous blood was drawn after an overnight fast at baseline and blood samples were deep frozen at -20 degrees Celsius. In addition to routinelaboratory analyses baseline total calcium (CaT, laboratory reference values = 2.15-2.51 nmol/l), PTH (laboratory reference values = 10-75 ng/l) (21), and 25-OHD (laboratory reference values > 40 nmol/l) (22) levels were measured and apolipoprotein E4 genotype (APOE4) was determined. CaT was determined by colorimetric assay with end-point determination and sample blank using Roche Diagnostics reagents (Cat. no. 1730240) and Modular-analyzer (Hitachi Ltd, Tokyo, Japan). The method is accreditated by FINAS Accreditation (SFS-EN ISO/IEC 17025:2005 and SFS-EN ISO 15189:2003). The PTH levels were determined with a solid-phase, two-site chemiluminescent enzyme-labelled immunometric assay (Immulite 2000 intact PTH). High performance liquid chromatography was used to measure plasma 25-OHD levels. APOE allele genotyping was performed from serum samples by immunoelectrophoresis and isoelectric focusing.

Data were analyzed with PASW Statistics 18 (SPSS Inc., Chicago). The statistical differences in baseline characteristics of subjects were determined by T-test or oneway ANOVA (continuous variables) and by chi-square test (dichotomous variables). Non-parametric tests (Mann-Whitney U or Kruskal-Wallis) were used when appropriate. A series of univariate and multivariate logistic regression models were created to calculate the adjusted risk ratios and 95% confidence intervals for the predictors of cognitive decline. Covariates were entered one by one in the models and no covariates were removed. P-values below 0.05 were considered as statistically significant.

Results

The patients were old (80 ± 5 years) and women outnumbered men (65% vs. 35%). The mean baseline MMSE score was 26 ± 3 and that of total CERAD score 69 ± 12. The baseline PTH levels varied from 9.3 ng/l to 497.3 ng/l (quartile cut-points: 38.7 ng/l, 59.0 ng/l, and 83.1 ng/l), the respective figures being 9.0 nmol/l and 128.0 nmol/l for 25-OHD (quartile cut-points: 32.0, 44.0, and 63.0 nmol/l). PTH and 25-OHD concentration correlated inversely ($r = -0.280$, $p < 0.001$). The baseline 25-OHD levels varied between 9-90 nmol/l in subjects with elevated baseline PTH (> 75ng/l).

At baseline a weak inverse association was observed between PTH levels and CERAD total scores ($r = -0.120$, $p = 0.023$), but the associations of PTH with MMSE and CDR were insignificant. In addition to total CERAD

Table 1

Baseline characteristics of patients by parathyroid hormone quartiles (cut-points: 38.7, 59.0, and 83.1 ng/l)

Variable	Quartile I	Quartile II	Quartile III	Quartile IV	P-value
Number	92	92	92	92	
Age, years	78.8±4.3	79.5±4.8	80.7±5.2	81.2±4.6	0.003
Female, %	75.3	63.0	57.6	64.8	0.083
Low education, %	52.7	58.7	65.2	54.9	0.333
Body mass index, kg/m^2	26.4±3.8	26.2±4.4	26.6±4.2	27.0±4.5	0.634
MMSE[a]	26.3±2.5	26.8±2.4	26.1±3.0	26.1±2.5	0.263
CDR[b] = 0, %	86.4	87.5	77.9	79.7	0.323
CERAD[c] total score	72.5±11.2	68.7±12.3	67.3±11.4	68.8±12.7	0.024
Apolipoprotein E allele 4, %	28.6	31.5	36.3	25.0	0.409
25-hydroxyvitamin D, nmol/l	55.0±22.3	49.9±21.9	46.7±20.7	38.6±18.1	<0.001
Total calcium[d], mmol/l	2.29±0.09	2.30±0.09	2.30±0.09	2.30±0.14	0.996
Creatinine, μmol/l	89.3±13.1	94.3±19.5	96.3±18.0	108.6±41.6	<0.001
GFR[e], ml/min	52.5±13.1	51.2±13.4	50.9±13.4	47.6±16.7	0.120

a. Mini mental state examination; b. Clinical dementia rating total score (0=no cognitive impairment); c. Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery total score; d. Number in quartiles = 79 / 81 / 82 / 85; e. Glomerular filtration rate according to Cockroft-Gault

Table 2

Baseline characteristics of patients by 25-hydroxyvitamin D quartiles (cut-points: 32.0, 44.0, and 63.0 nmol/l)

Variable	Quartile I	Quartile II	Quartile III	Quartile IV	P-value
Number	90	92	93	93	
Age, years	80.7±5.3	79.7±4.4	79.8±4.9	79.9±4.6	0.499
Female, %	62.2	70.7	60.2	67.7	0.417
Low education, %	52.2	65.2	58.1	55.9	0.339
Body mass index, kg/m^2	27.7±5.0	26.5±3.9	26.5±4.0	25.5±3.6	0.006
MMSE[a]	26.1±2.6	26.0±2.6	26.4±2.7	26.7±2.6	0.338
CDR[b] = 0, %	82.4	77.8	88.0	84.1	0.423
CERAD[c] total score	68.5±12.2	68.7±11.7	70.1±12.2	69.3±12.1	0.734
Apolipoprotein E allele 4, %	31.0	33.0	30.1	27.5	0.880
Parathyroid hormone, ng/l	92.6±72.4	69.5±47.0	60.7±35.4	53.4±30.9	<0.001
Total calcium[d], mmol/l	2.26±0.11	2.29±0.11	2.31±0.09	2.32±0.11	0.007
Creatinine, μmol/l	100.9±36.7	94.7±19.2	98.4±27.2	94.6±18.5	0.295
GFR[e], ml/min	52.0±16.2	50.5±13.8	51.1±13.7	48.6±13.3	0.431

a. Mini mental state examination; b. Clinical dementia rating (0=no cognitive impairment); c. Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery total score; d Number in quartiles = 76 / 83 / 84 / 84; e. Glomerular filtration rate according to Cockroft-Gault

Table 3

Three-year unadjusted predictive value (OR, 95%CIs) of parathyroid hormone and 25-hydroxyvitamin D by baseline quartiles (quartile I as reference) for a minimum of 10 point decline in Consortium to Establish a Registry for Alzheimer Disease neuropsychological assessment battery total score (CERAD), a minimum of 4 point decline in Mini Mental State Examination (MMSE), and any worsening of Clinical Dementia Rating (CDR)

	Quartile I	Quartile II	Quartile III	Quartile IV
	Baseline parathyroid hormone (quartile cut-points: 38.7, 59.0, and 83.1 ng/l)			
10 point decline in CERAD[a]	1.00	0.91, 0.28-2.97	1.17, 0.37-3.68	2.08, 0.71-6.14
Any increase in CDR[b]	1.00	5.42, 1.12-26.3	5.90, 1.22-28.66	6.48, 1.33-31.54
4 point decline in MMSE[c]	1.00	2.03, 0.66-6.28	2.92, 0.98-8.70	3.14, 1.04-9.49
	Baseline 25-hydroxyvitamin D (quartile cut-points: 32.0, 44.0, and 63.0 nmol/l)			
10 point decline in CERAD[d]	1.00	1.38, 0.43-4.49	1.68, 0.55-5.12	0.90, 0.25-3.27
Any increase in CDR[e]	1.00	0.77, 0.26-2.29	0.92, 0.34-2.53	0.45, 0.13-1.59
4 point decline in MMSE[f]	1.00	0.86, 0.34-2.16	0.57, 0.22-1.49	0.70, 0.27-1.84

a. Number in quartiles = 66 / 72 / 67 / 58, total number = 263; b. Number in quartiles = 61 / 58 / 54 / 50, total number = 223; c. Number in quartiles = 69 / 73 / 70 /61, total number = 273; d. Number in quartiles = 56 / 67 / 78 / 62, total number = 263; e. Number in quartiles = 40 / 55 / 67 / 51, total number = 223; f. Number in quartiles = 60 / 68 / 79 / 66, total number = 273

Table 4

Three-year predictive value (OR, 95%CIs) of high baseline parathyroid hormone (> 83.1 ng/l) and low baseline 25-hydroxyvitamin D (< 32 nmol/l) in series of multivariate analyses for a minimum of 10 point decline in Consortium to Establish a Registry for Alzheimer Disease neuropsychological assessment battery total score (CERAD), a minimum of 4 point decline in Mini Mental State Examination (MMSE), and any worsening of Clinical Dementia Rating (CDR)

	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
	Baseline parathyroid hormone ≥ 83.1 ng/l (Quartile IV vs. Quartiles I-III)			
10 point decline in CERAD	2.37, 1.05-5.35	2.38, 1.04-5.41	2.87, 1.22-6.76	3.56, 1.36-9.46
4 point decline in MMSE	1.57, 0.75-3.3	1.46, 0.68-3.1	1.41, 0.64-3.12	1.46, 0.59-3.60
Any increase in CDR	1.96, 0.85-4.55	1.78, 0.76-4.16	2.01, 0.82-4.89	2.10, 0.77-5.74
	Baseline 25-hydroxyvitamin D < 32.0 nmol/l (Quartile I vs. Quartile II-IV)			
10 point decline in CERAD	0.75, 0.27-2.06	0.74, 0.27-2.05	0.76, 0.27-2.14	0.27, 0.06-1.25
4 point decline in MMSE	1.42, 0.67-3.05	1.35, 0.62-2.95	1.32, 0.59-2.98	0.94, 0.35-2.51
Any increase in CDR	1.38, 0.57-3.33	1.29, 0.53-3.17	1.42, 0.56-3.60	1.17, 0.39-3.51

a. Unadjusted, N = 263 / 273 / 223 for CERAD / MMSE / CDR; b. Adjusted for age and gender, N = 263 / 273 / 223 for CERAD / MMSE / CDR; c. Adjusted for age, gender, education, apolipoprotein E4, and baseline cognition test score, N = 260 / 270 / 221 for CERAD / MMSE / CDR; d. Adjusted for age, gender, education, apolipoprotein E4, baseline cognition test score, intervention group, body mass index, creatinine, total calcium, and parathyroid hormone or 25-hydroxyvitamin D, N = 232 / 241 / 198 for CERAD / MMSE / CDR

scores and 25-OHD levels, PTH concentrations associated positively with age and renal function (Table 1). However, the statistical significance of the baseline association between total CERAD scores and PTH was lost after controlling age, gender, education, apolipoprotein E4, body mass index, creatinine, total calcium, and 25-hydrovitamin D (data not shown). In addition to PTH concentrations 25-OHD levels associated inversely with body mass index and CaT (Table 2). However, no significant associations were found between 25-OHD and the three cognition tests at baseline.

There was a consistent trend by increasing quartile of baseline PTH for increased risk of clinically significant three-year cognitive decline regardless of the cognition test (Table 3). When the highest baseline PTH levels (PTH > 83.1 ng/l, IV-quartile) were compared with others (quartiles I-III), high baseline PTH associated significantly with 2.4-fold risk (95%CIs = 1.05-5.35, p = 0.038) of a minimum of 10-point decline in CERAD total score within the three-year follow-up (Table 4). Furthermore, the increased risk for clinically meaningful decline in CERAD total score remained significant after controlling for age, gender, education, apolipoprotein E4, baseline total CERAD score, body mass index, creatinine, total calcium, and 25-hydrovitamin D (Table 4). No consistent tendencies or statistical significances were found for cognitive decline within the three-year follow-up, when patients were stratified according to baseline 25-OHD quartiles (Tables 3 and 4).

Discussion

This prospective follow-up study shows that high baseline PTH concentrations are associated with clinically significant cognitive decline independently of baseline vitamin D status in community-dwelling older people with a history of vascular diseases. This observation accords well with the results of our previous study (11). The results of the present study support the observations of the parathyroidectomy trials showing improvements in cognitive functions (14-16).

The design of this study does not shed light on the possible pathogenetic role of PTH, but some mechanisms can be suggested. Although PTH does not cross the undamaged blood brain barrier (23), in conjunction with other mediators leading to disturbed blood brain barrier permeability, PTH may be involved in brain cell damage. In vitro studies have shown that PTH increases intracellular Ca2+ concentration and causes cell deterioration in rat's hippocampal slices (24). PTH receptors are abundant across the central nervous system in humans (25). Dysregulation of intracellular Ca2+ homeostasis in the hippocampal neurons plays an important role in the pathogenesis of cognitive decline (26). Individual differences in the cell membrane's ability to resist calcium influx may be hypothesized to cause the well-known but poorly understood variability in clinical symptoms in patients with elevated PTH. Furthermore, one of the key regulators of parathyroid activity, namely peptidyl-prolyl isomerase Pin1 (27), has been associated with Alzheimer's disease (28). However, the increase in PTH may be a marker for individual vitamin D insufficiency i.e. the serum concentration of 25-OHD below which PTH increases varies greatly between subjects. In the present study, the baseline 25-OHD levels varied between 9-90 nmol/l in subjects with elevated baseline PTH (> 75ng/l).

Few previous vitamin D supplementation trials have addressed its effects on cognitive function. In a double blind randomized placebo controlled trial of six-week cholecalciferol (5000 IU/d) supplementation in young healthy adults (N =128) no effect was found (29). Again, the role of parathyroid function was not assessed. In an

open label clinical study of older vitamin D deficient nursing home residents a four week ergocalciferol (≈ 2000 IU/d) supplementation decreased PTH concentrations, but no effects on cognitive functions was observed within the short follow-up period (30). However, modest differences in cognitive changes have been reported in older outpatients visiting a memory clinic (N = 44) in a retrospective pre-post cohort study (31). In that study the dose of cholecalciferol supplementation ranged from 800 IU/d to 100000 IU/month and the treatment allocation was neither randomized nor blinded.

The study design is the major strength of this study. The patients were recruited from a population based sample of older people. The recruited patients were thoroughly examined by a geriatrician-internist at baseline. Cognition was assessed with CERAD, which is a more comprehensive method than MMSE or CDR. Furthermore, the 25-OHD concentrations were determined by high performance liquid chromatography. This study has also some weaknesses. The observational nature of the study does not allow the evaluation of causality of the associations. Even though the study protocol did not include systematic use of vitamin D supplementation and baseline 25-OHD and PTH levels were measured after the completion of the follow-up period, the lack of detailed data on the use of vitamin D supplementation during follow-up should be considered as a weakness of this study. Furthermore, data on ionized calcium and novel regulators of parathyroid function were not available. Missing follow-up data, particularly, resulted in attrition of the study population in the multifactorial analyses. Thus, the lack of association between baseline vitamin D and cognition should be interpreted with caution. However, to the best of our knowledge this is the first prospective follow-up study to investigate the predicitive value of both 25-OHD and PTH for cognitive decline in a relatively large sample of community-dwelling older people.

In conclusion, high levels of PTH are associated independently of vitamin D status with clinically significant cognitive decline in older community-dwelling people with a history of vascular diseases. Further studies are warranted to address the role of PTH and its regulators in the etiology of cognitive impairment.

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References

1. Pearce SH, Cheetham TD. Diagnosis and management of vitamin D deficiency. BMJ. 2010;340:b5664.
2. McCann JC, Ames BN. Is there convincing biological or behavioral evidence linking vitamin D deficiency to brain dysfunction? FASEB J. 2008;22:982-1001.
3. Balion C, Griffith LE, Strifler L, et al. Vitamin D, cognition, and dementia: A systematic review and meta-analysis. Neurology. 2012;79:1397-405.
4. McGrath J, Scragg R, Chant D, Eyles D, Burne T, Obradovic D. No association between serum 25-hydroxyvitamin D3 level and performance on psychometric tests in NHANES III. Neuroepidemiology. 2007;29:49-54.
5. Jorde R, Waterloo K, Saleh F, Haug E, Svartberg J. Neuropsychological function in relation to serum parathyroid hormone and serum 25-hydroxyvitamin D levels. The Tromsø study. J Neurol. 2006;253:464-470.
6. Kipen E, Helme RD, Wark JD, Flicker L. Bone density, vitamin D nutrition, and parathyroid hormone levels in women with dementia. J Am Geriatr Soc. 1995;43:1088-1091.
7. Llewellyn DJ, Lang IA, Langa KM, et al. Vitamin D and risk of cognitive decline in elderly persons. Arch Intern Med. 2010;170:1135-41.
8. Slinin Y, Paudel M, Taylor BC, et al.; for the Study of Osteoporotic Fractures Research Group. Association Between Serum 25(OH) Vitamin D and the Risk of Cognitive Decline in Older Women. J Gerontol A Biol Sci Med Sci. 2012;[Epub ahead of print]
9. Annweiler C, Rolland Y, Schott AM, Blain H, Vellas B, Beauchet O. Serum Vitamin D Deficiency as a Predictor of Incident Non-Alzheimer Dementias: A 7-Year Longitudinal Study. Dement Geriatr Cogn Disord. 2012;32:273-278.
10. Slinin Y, Paudel ML, Taylor BC, et al.; Osteoporotic Fractures in Men (MrOS) Study Research Group. 25-Hydroxyvitamin D levels and cognitive performance and decline in elderly men. Neurology. 2010;74:33-41.
11. Björkman MP, Sorva AJ, Tilvis RS. Does elevated parathyroid hormone concentration predict cognitive decline in older people? Aging Clin Exp Res. 2010;22:164-169.
12. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology. 1989;39:1159-1165.
13. Rossetti HC, Munro Cullum C, Hynan LS, Lacritz LH. The CERAD Neuropsychologic Battery Total Score and the progression of Alzheimer disease. Alzheimer Dis Assoc Disord. 2010;24:138-142.
14. Burney RE, Jones KR, Christy B, Thompson NW. Health status improvement after surgical correction of primary hyperparathyroidism in patients with high and low preoperative calcium levels. Surgery 1999;125:608-614.
15. Chou FF, Chen JB, Hsieh KC, Liou CW. Cognitive changes after parathyroidectomy in patients with secondary hyperparathyroidism. Surgery 2008;143:526-532.
16. Babińska D, Barczyński M, Stefaniak T, et al. Evaluation of selected cognitive functions before and after surgery for primary hyperparathyroidism. Langenbecks Arch Surg. 2012;397:825-831.
17. Strandberg TE, Pitkala K, Berglind S, Nieminen MS, Tilvis RS. Multifactorial cardiovascular disease prevention in patients aged 75 years and older: A randomized controlled trial: Drugs and Evidence Based Medicine in the Elderly (DEBATE) Study. Am Heart J. 2001;142:945-951.
18. Strandberg TE, Pitkala KH, Berglind S, Nieminen MS, Tilvis RS. Multifactorial intervention to prevent recurrent cardiovascular events in patients 75 years or older: the Drugs and Evidence-Based Medicine in the Elderly (DEBATE) study: a randomized, controlled trial. Am Heart J. 2006;152:585-592.
19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.
20. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for staging of dementia. Br J Psychiatry 1982;140:566-572.
21. Kao PC, van Heerden JA, Grant CS, Klee GG, Khosla S. Clinical performance of parathyroid hormone immunometric assays. Mayo Clin Proc 1992; 67: 637–645.
22. Turpeinen U, Hohenthal U, Stenman U-H. Determination of 25-Hydroxyvitamin D in serum by HPLC and immunoassay. Clin Chem 2003; 49: 1521–1524.
23. Akmal M, Tuma S, Goldstein DA, Pattabhiraman R, Bernstein L, Massry SG. Intact and carboxyterminal PTH do not cross the blood-cerebrospinal fluid barrier. Proc Soc Exp Biol Med 1984;176:434-437.
24. Hirasawa T, Nakamura T, Mizushima A, et al. Adverse effects of an active fragment of parathyroid hormone on rat hippocampal organotypic cultures. Br J Pharmacol 2000;129:21-28.
25. Reppe S, Stilgren L, Abrahamsen B, et al. Abnormal muscle and hematopoietic gene expression may be important for clinical morbidity in primary hyperparathyroidism. Am J Physiol Endocrinol Metab. 2007;292:E1465-E1473.
26. Thibault O, Gant JC, Landfield PW. Expansion of the calcium hypothesis of brain aging and Alzheimer's disease: minding the store. Aging Cell 2007;6:307-317.
27. Naveh-Many T. Minireview: the play of proteins on the parathyroid hormone messenger ribonucleic Acid regulates its expression. Endocrinology. 2010;151:1398-1402.
28. Driver JA, Lu KP. Pin1: a new genetic link between Alzheimer's disease, cancer and aging. Curr Aging Sci. 2010;3:158-165.
29. Dean AJ, Bellgrove MA, Hall T, et al. Effects of vitamin D supplementation on cognitive and emotional functioning in young adults--a randomised controlled trial. PLoS One. 2011;6:e25966.
30. Przybelski R, Agrawal S, Krueger D, Engelke JA, Walbrun F, Binkley N. Rapid correction of low vitamin D status in nursing home residents. Osteoporos Int. 2008;19:1621-1628.
31. Annweiler C, Fantino B, Gautier J, Beaudenon M, Thiery S, Beauchet O. Cognitive effects of vitamin d supplementation in older outpatients visiting a memory clinic: a pre-post study. J Am Geriatr Soc. 2012;60:793-795.