Published in final edited form as:
Mov Disord. 2013 July ; 28(8): . doi:10.1002/mds.25405.

The Relationship between Balance Control and Vitamin D in Parkinson's Disease—A Pilot Study

Amie L. Peterson, MD[1,2,*], **Martina Mancini, PhD**[1], and **Fay B. Horak, PT, PhD**[1]

[1]Parkinson's Center of Oregon, Oregon Health and Science University, Portland, Oregon, USA

[2]Parkinson's Disease Research and Education Center, Portland Veterans Affairs Hospital, Portland, Oregon, USA

Abstract

Background—Balance problems and falls are a major source of morbidity and mortality in patients with Parkinson's disease. Vitamin D supplementation reduces falls and sway in neurologically intact elderly fallers, but effects in Parkinson's disease are not established.

Methods—To study this relationship and select outcome measures for a vitamin D intervention study, balance function and vitamin D concentration were quantified in a series of Parkinson's patients in a cross-sectional, observational study. Participants underwent a battery of 5 balance tests.

Results—Serum vitamin D concentrations were correlated inversely with Parkinson's severity, as measured by the motor Unified Parkinson's Disease Rating Scale. Among the balance measures, vitamin D concentrations were correlated with automatic posture responses to backwards translation, specifically with response strength and stance weight asymmetry.

Conclusions—These findings support the hypothesis that vitamin D plays a role in balance among patients with Parkinson's disease and identify specific outcome measures for detecting effects of vitamin D upon balance.

Keywords

Parkinson's disease; vitamin D; accidental falls

Postural instability is 1 of the 4 cardinal features of Parkinson's disease (PD) and is a major source of morbidity and mortality late in the disease. Research shows that vitamin D supplementation reduces falls and decreases sway in elderly fallers.[1,2] We investigated the relationship between vitamin D and balance (using clinical posturography) in patients with PD. The 2 primary aims of this study were (1) to gain insight into the relationship between vitamin D concentration and balance control and (2) to determine appropriate gait and balance tests for a vitamin D intervention study.

*Corresponding author: Dr. A. Peterson, Parkinson's Center of Oregon, Mail Code: OP-32, Oregon Health and Science University, 3181 S.W. Sam Jackson Park Road, Portland, OR 97239-3098; peterami@ohsu.edu.

Relevant conflicts of interest/financial disclosures:

Full financial disclosures and author roles may be found in the online version of this article.

NIH-PA Author Manuscript
NIH-PA Author Manuscript

Patients and Methods

Study Population

This was a cross-sectional, observational study. Forty participants were recruited from Oregon Health and Sciences University (OHSU) and the Portland Veterans Affairs Hospital between October 2008 and January 2010 (mean ± standard deviation: age, 67 ± 9.6 years; Hoehn and Yahr stage, 2.6 ± 0.47; motor United Parkinson's Disease Rating Scale [mUPDRS] score, 20.8 ± 9.3). This number was based on an 80% power to detect a correlation ≥0.43. PD diagnosis was confirmed by a movement disorders neurologist using National Institute of Neurological Disorders and Stroke criteria.[3] Inclusion criteria included the ability to ambulate without the assistance of another person and the ability to cooperate with balance and cognitive testing. Participants could not have significant cognitive (Mini-Mental Status Examination [MMSE] scores <25)[4] or other neurological or orthopedic deficit that, in the investigator's opinion, would have a significant impact on gait and cognition (e.g. stroke, fracture). Serum could not be obtained from 1 participant, and he was removed from the study before undergoing balance testing.

Protocol

Balance assessment—All assessments occurred in the "on" state, approximately 1 hour after taking PD medications. The Neurocom Clinical Research System (Neurocom, Clackamas, OR) was used for all testing. Participants attempted 5 tests, but many were only able to complete the first 3 tests.

(1) Backward translation as part of the Motor Control Test (MCT) assesses the ability to quickly recover equilibrium after an unexpected external disturbance (backward perturbation), like what occurs during a slip. This is termed the automatic postural response. **(2) The Sensory Organization Test** (SOT) measures body sway under 6 sensory conditions: eyes open, eyes closed, moveable visual surround with the platform stable, then the same 3 conditions with the platform moving in response to the participant's movements (sway referenced) (see Fig. 1C). The SOT has demonstrated sensitivity to the risk of falling.[5,6] **(3) The Sit to Stand test** (STS) quantifies the participant's ability to rise from a seated to a standing position.

Approximately half of the participants were not able to complete the **Walk and Turn** test, which requires the participant to pivot turn on a narrow platform. Many participants were at risk of injury from falling off the narrow platform. No participants were able to complete **the Unilateral Stance Eyes Open and Closed** test, which requires standing on 1 leg for 10 seconds with eyes first open and then closed.

Other assessments—Serum was collected and frozen at the study visit. At the conclusion of the study, 25-hydroxyvitamin D levels were measured in all samples. Cognitive testing included the MMSE, Trail Making Test parts A and B, verbal fluency for animals, and 5-point clock draw.[4,7–9] The mUPDRS and the modified Abnormal Involuntary Movement Scale (mAIMS) were completed.[10,11] Participants were asked about their prescription and over-the-counter supplements and medications.

Statistical Analysis

The normal distribution of data was tested with the Kolmogorov-Smirnov test. Correlation coefficients were calculated first without adjustment for confounding variables and again adjusting for age and mUPDRS scores (partial correlation). In particular, Pearson product-moment correlation was used to assess the relationship between vitamin D concentration and extracted variables in each SOT condition and in the backward translation (MTC) and STS tests. Pearson product-moment correlation also was used to assess the relationship between participant age and vitamin D concentration as well as mUPDRS score and vitamin D concentration. Correction was not made for multiple comparisons. Algorithms for statistical evaluation were written in Matlab software (The MathWorks, Inc., Natick, MA).

Results

Vitamin D Concentrations Correlated with Symptom Severity

Vitamin D concentration and PD symptom severity (mUPDRS) had a significant negative correlation ($r = -0.33$; $P = 0.04$). This relationship remained when adjusting for age (see Fig. 2A). The vitamin D concentration did not significantly correlate with Hoehn and Yahr score ($r = -0.39$; $P = 0.69$).

Relationship Between MCT and Vitamin D Concentrations

The strongest correlation of postural tasks with vitamin D was with automatic postural responses measured with the MCT (see Fig. 1A). Response strength and the symmetry of postural responses were correlated with vitamin D concentrations.

Vitamin D Concentrations Correlated Only with Condition 4 of the SOT

Vitamin D concentrations were correlated inversely with condition 4 of the SOT (eyes open, sway referenced) (see Fig. 1C,D). No significant correlations were observed with conditions 1, 2, 3, 5, or 6 of the SOT or in the S2S.

Discussion

Serum Vitamin D Concentrations Correlated with Symptom Severity

Vitamin D concentrations were correlated with PD symptom severity. Prior studies have demonstrated lower vitamin D concentrations in patients with later stage PD and in patients with PD versus those with Alzheimer's and controls.[12,13] It is possible that individuals who have more severe PD are less ambulatory, get less sun exposure, and subsequently have lower levels of vitamin D. It is also possible that vitamin D has an effect on PD symptoms. The presence of the final converting enzyme and receptors for vitamin D throughout the brain suggests that vitamin D may act directly on the central nervous system.[14] Using immunostaining to examine 11 brain regions, the substantia nigra was the only area that was very intensely immunoreactive for both the receptor and the enzyme. The caudate/putamen stained intensely for both. Potential mechanisms of action include the up-regulation of glial cell-derived neurotropic factor (GDNF) and stabilization of mitochondrial function.[15,16]

Serum Vitamin D Concentrations Correlated with Automatic Postural Responses during the MCT

The correlations between symmetry of automatic postural responses as measured by the MCT and vitamin D concentrations are novel findings. In the absence of correction for multiple comparisons, the statistical significance is marginal. However, the finding that it is present even when correcting for symptom severity and that it is significant in the small, medium, and large perturbations suggests that a true relationship exists.

Automatic postural responses are extremely important in balance control. The majority of falls in elderly persons are due to a trip or slip—the action mimicked by the platform moving backward in the MCT.[17] Latency of postural responses are normal in patients with PD, but they activate inappropriate muscles in addition to the muscles needed to respond to the perturbation, resulting in smaller and overall slower forces to recover equilibrium.[18]

Postural responses are symmetric in healthy individuals; but, in our PD participants, we found a correlation between the degree of asymmetry and the vitamin D concentration.

Serum Vitamin D Concentrations Only Correlate with One Measure of Postural Sway: SOT4

We were somewhat surprised that vitamin D concentrations correlated with only 1 measure of sway on the SOT4. A number of intervention studies have demonstrated a decrease in postural sway (equivalent to SOT items 1 and 2) with vitamin D supplementation in non-PD populations.[1,2] Other studies, however, demonstrated no significant improvements in sway, improvements in only a subset with poorer baseline balance, or no additional improvement over calcium alone.[19,20] It is possible that there is a relationship between sway and vitamin D in PD but that we were not able to detect it, because too many other factors affected balance. It is also possible that vitamin D and balance have a different relationship in persons with PD than in elderly, non-PD fallers. All testing was done in the “on” state, which could affect results. We made this choice primarily because, from a clinically meaningful perspective, changes in balance/gait during the “on” state are what most people desire. It is also believed that gait/balance symptoms are affected less by levodopa than other Parkinson’s symptoms.

Hypotheses for Vitamin D’s Mechanism of Effect on Automatic Postural Responses

There are multiple theoretical mechanisms by which vitamin D could have an effect on automatic postural responses. The most commonly cited theory for the connection between falls and vitamin D is through muscular strength. It is know that severe vitamin D deficiency can cause a myopathy.[21] The activation of vitamin D receptors in muscle leads to protein synthesis, muscle cell growth, and improved muscle function. Clinical studies have shown improvements in strength after vitamin D supplementation in vitamin D-deficient individuals. Automatic postural responses, however, are extremely complex, involving much more than muscle strength. There are short, medium, and long latency components of postural responses, suggesting a role for the spinal cord, midbrain/brainstem, and cerebellum/basal ganglia/cerebral cortex, respectively.[22,23] Vitamin D receptors have been identified in all of these brain areas in human brains and also in rat spinal cords.[14,24] It is known that vitamin D plays a role in regulating over 200 genes as well as in more rapid cellular responses, including alterations in cytosolic calcium, phosphoinositide turnover, protein kinase C subcellular distribution, and activation of Map kinases; therefore, a specific neural mechanism for the effects of vitamin D on postural response is difficult to determine.[25,26]

Conclusions

Our data support a relationship between vitamin D and balance and between vitamin D and PD symptom severity and are informative for future study design. The relationship between PD symptom severity and vitamin D concentrations is particularly interesting. Future intervention studies should include measures of symptom severity and postural responses and should track possible changes with vitamin D supplementation.

There are clear limitations to this study. Because it was a cross-sectional study, causality cannot be concluded. Also, also multiple comparisons were made, limiting the statistical strength of the relationships observed. The relevance of these data is in informing future studies of vitamin D and falls, adding support for intervention studies that specifically examine the effects of vitamin D supplementation on falls in PD.

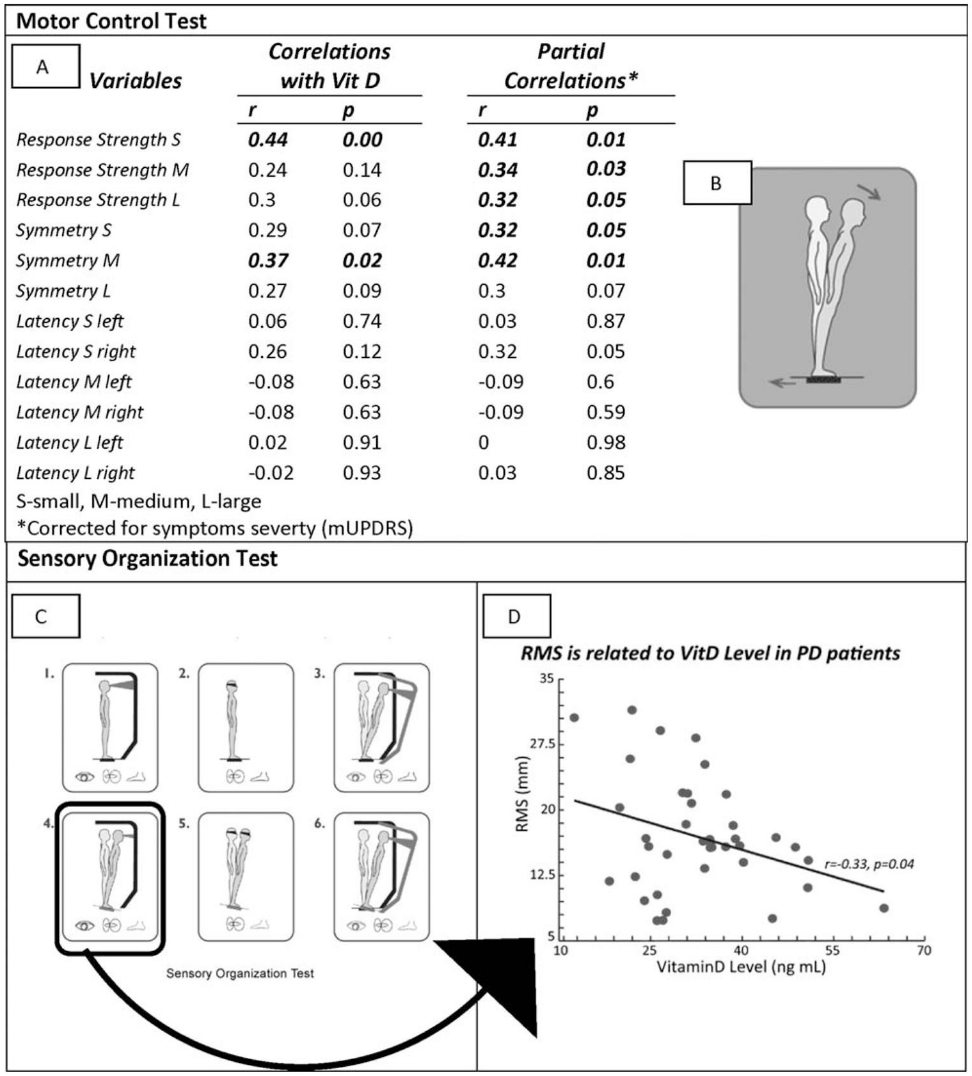
Acknowledgments

Funding agencies: PSG Mentored Clinical Research Award supported by the Parkinson's Study Group and Pakrinson's Disease Foundation Advancing Parkinson's Treatments Innovations Grant. The Department of Veteran's Affairs Career development award - The effects of vitamin D on balance in persons with Parkinson's. The Oregon Clinical and Translation Research Institute (OCTRI), grant number UL1 RR024140 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. UDALL - NIH P3NS062684. Portland VA PADRECC.

References

1. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporosis Int. 2009; 20:315–322.
2. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res. 2000; 15:1113–1118. [PubMed: 10841179]
3. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. Arch Neurol. 1999; 56:33–39. [PubMed: 9923759]
4. Tombaugh TN, McIntyre NJ. The Mini-Mental State Examination: a comprehensive review. J Am Geriatr Soc. 1992; 40:922–935. [PubMed: 1512391]
5. Buatois S, Gueguen R, Gauchard GC, Benetos A, Perrin PP. Posturography and risk of recurrent falls in healthy non-institutionalized persons aged over 65. Gerontology. 2006; 52:345–352. [PubMed: 16905886]
6. Whitney SL, Marchetti GF, Schade AI. The relationship between falls history and computerized dynamic posturography in persons with balance and vestibular disorders. Arch Phys Med Rehabil. 2006; 87:402–407. [PubMed: 16500176]
7. Adjutant General's Office. War Department. Manual of Directions and Scoring. Washington, DC: Adjutant General's Office; 1944. Army Individual Test Battery.
8. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. Arch Clin Neuropsychol. 1999; 14:167–177. [PubMed: 14590600]
9. Nishiwaki Y, Breeze E, Smeeth L, Bulpitt CJ, Peters R, Fletcher AE. Validity of the clock-drawing test as a screening tool for cognitive impairment in the elderly. Am J Epidemiol. 2004; 160:797–807. [PubMed: 15466502]
10. Fahn, S.; Goldstein, M.; Calne, DB. UPDRS Program Members. Recent Developments in Parkinson's Disease. Vol. 2. Florham Park, NJ: Macmillan Healthcare Information; 1987. Unified Parkinson's Disease Rating Scale; p. 153-163.
11. May PR, Lee MA, Bacon RC. Quantitative assessment of neuroleptic-induced extrapyramidal symptoms: clinical and nonclinical approaches. Clin Neuropharmacol. 1983; 6(suppl 1):S35–S51. [PubMed: 6139165]
12. Evatt ML, Delong MR, Khazai N, Rosen A, Triche S, Tangpricha V. Prevalence of vitamin d insufficiency in patients with Parkinson disease and Alzheimer disease. Arch Neurol. 2008; 65:1348–1352. [PubMed: 18852350]
13. Sato Y, Kikuyama M, Oizumi K. High prevalence of vitamin D deficiency and reduced bone mass in Parkinson's disease. Neurology. 1997; 49:1273–1278. [PubMed: 9371907]
14. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. J Chem Neuroanat. 2005; 29:21–30. [PubMed: 15589699]
15. Sanchez B, Lopez-Martin E, Segura C, Labandeira-Garcia JL, Perez-Fernandez R. 1,25-dihydroxyvitamin D(3) increases striatal GDNF mRNA and protein expression in adult rats. Brain Res Mol Brain Res. 2002; 108(1–2):143–146. [PubMed: 12480187]
16. Li L, Prabhakaran K, Zhang X, Zhang L, Liu H, Borowitz JL, Isom GE. 1Alpha,25-dihydroxyvitamin D3 attenuates cyanide-induced neurotoxicity by inhibiting uncoupling protein-2 up-regulation. J Neurosci Res. 2008; 86:1397–1408. [PubMed: 18183618]

17. Black, SE.; Maki, BE.; Fernie, GR. Aging, imbalance, and falls. In: Sharpe, JA.; Barber, HO., editors. The Vestibulo-Ocular Reflex and Vertigo. New York, NY: Raven Press; 1993. p. 317-335.
18. Horak FB, Henry SM, Shumway-Cook A. Postural perturbations: new insights for treatment of balance disorders. Phys Ther. 1997; 77:517–533. [PubMed: 9149762]
19. Annweiler C, Schott AM, Berrut G, Fantino B, Beauchet O. Vitamin D-related changes in physical performance: a systematic review. J Nutr Health Aging. 2009; 13:893–898. [PubMed: 19924350]
20. Boonen S, Bischoff-Ferrari HA, Cooper C, Lips P, Ljunggren O, Meunier PJ, Reginster JY. Addressing the musculoskeletal components of fracture risk with calcium and vitamin D: a review of the evidence. Calcif Tissue Int. 2006; 78:257–270. [PubMed: 16622587]
21. Pfeifer M, Begerow B, Minne HW. Vitamin D and muscle function. Osteoporosis Int. 2002; 13:187–194.
22. Asaka T, Yahata K, Mani H, Wang Y. Modulations of muscle modes in automatic postural responses induced by external surface translations. J Mot Behav. 2011; 43:165–172. [PubMed: 21400330]
23. Torres-Oviedo G, Ting LH. Muscle synergies characterizing human postural responses. J Neurophysiol. 2007; 98:2144–2156. [PubMed: 17652413]
24. Prufer K, Veenstra TD, Jirikowski GF, Kumar R. Distribution of 1,25-dihydroxyvitamin D3 receptor immunoreactivity in the rat brain and spinal cord. J Chem Neuroanat. 1999; 16:135–145. [PubMed: 10223312]
25. Holick MF. Vitamin D deficiency. N Engl J Med. 2007; 357:266–281. [PubMed: 17634462]
26. Sitrin MD, Bissonnette M, Bolt MJ, et al. Rapid effects of 1,25(OH)2 vitamin D3 on signal transduction systems in colonic cells. Steroids. 1999; 64(1–2):137–142. [PubMed: 10323682]



Motor Control Test

A

Variables	Correlations with Vit D		Partial Correlations*	
	r	*p*	*r*	*p*
Response Strength S	***0.44***	***0.00***	***0.41***	***0.01***
Response Strength M	0.24	0.14	***0.34***	***0.03***
Response Strength L	0.3	0.06	***0.32***	***0.05***
Symmetry S	0.29	0.07	***0.32***	***0.05***
Symmetry M	***0.37***	***0.02***	***0.42***	***0.01***
Symmetry L	0.27	0.09	0.3	0.07
Latency S left	0.06	0.74	0.03	0.87
Latency S right	0.26	0.12	0.32	0.05
Latency M left	-0.08	0.63	-0.09	0.6
Latency M right	-0.08	0.63	-0.09	0.59
Latency L left	0.02	0.91	0	0.98
Latency L right	-0.02	0.93	0.03	0.85

S-small, M-medium, L-large

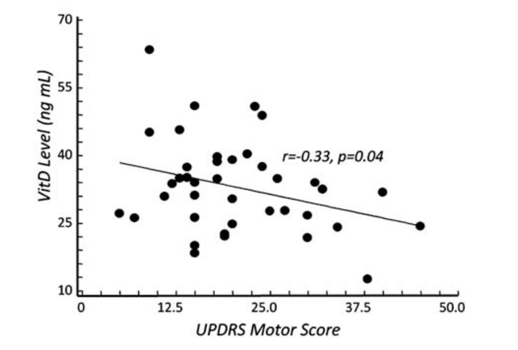
*Corrected for symptoms severty (mUPDRS)

FIG. 1.

(A) Correlations between vitamin D (VitD) concentrations and backward translation are illustrated. (**B,C**) The different conditions of the sensory organization test are illustrated. Only condition 4 (**D**) was correlated with vitamin D concentrations. RMS indicates root mean square – a measure of sway.

Correlation between vitamin D and symptom severity

A. Relationship between vitamin D and mUPDRS



B. Participant Characteristics*

Variable	TOTAL (N=40)
Age	67 (±9.6)
Gender (% female)	18 (45%)
Race (% Non-White)	1 (2.5%)
MMSE	29 (±1.1)
UPDRS (motor score)	20.8 (±9.3)
H&Y	2.6 (+0.47)
Vitamin D (ng/ml)	32.7 (±10.2)

*Values are Mean (±SD) or n (%), MMSE= Mini-Mental State Examination , UPDRS= Unified Parkinson's Disease Rating Scale

FIG. 2.

(**A**) The significant correlation between the motor United Parkinson's Disease Rating Scale (mUPDRS) and vitamin D (VitD) concentration is illustrated. Intervention studies are needed to further examine this relationship and determine causality. (**B**) Patients on average had moderate disease severity and vitamin D concentrations that were sufficient. MMSE indicates Mini-Mental State Examination; H&Y, Hoehn and Yahr staging; SD, standard deviation.