Title: A Pilot Study of Balance and Vitamin D in Persons with Parkinson's disease (PD)

Abstract
Vitamin D appears to reduce falls in elderly persons by unclear mechanisms. The primary goal of this pilot study is to see if there is a relationship between vitamin D levels and balance performance in persons with PD. Secondary goals are to gain more information on vitamin D levels and balance performance (as assessed using dynamic posturography) in this population. The information from this pilot study will help in design of an intervention study to test the hypothesis that vitamin D supplementation improves balance and reduces falls in persons with PD. This study will also allow for insight into the mechanism through which vitamin D effects falls and balance.

Specific Aims

1. To determine the relationship between low vitamin D levels, poor balance (measured via dynamic posturography), and falls in a population with PD.
2. To gather preliminary data on vitamin D levels in a population of subjects with PD and determine the prevalence of vitamin D deficiency.

Hypothesis
Vitamin D deficiency negatively impacts balance, as measured using dynamic posturography, and results in increased fall rates in persons with PD.

Background & Significance
PD is a disorder characterized by four cardinal features; tremor, rigidity, slowness, and poor balance. A prospective study by Wood et. al. in 2002 found that over 68% of persons with PD experienced at least one fall over the course of a year.[1] A recent meta-analysis estimated a 22% decrease in falls in person receiving vitamin D supplementation.[2]

It is traditionally hypothesized that vitamin D decreases falls through its affect on muscles, but a recent study showed that there also appears to be an improvement in balance.[3] Studies have shown that vitamin D receptors are present throughout the brain with a particularly high density in the substantia nigra, one of the primary areas of pathology in Parkinson's disease.[4] There are benefits of looking specifically at a population with PD. The known presence of vitamin D receptors in the brain suggests a central mechanism for effects on balance is very possible Persons with PD have balance problems with a central nervous system origin and subtle changes may be easier to detect as compared to a population with normal balance.

The data on the vitamin D levels will itself be informative and be important in designing the future intervention study. A recent study showed persons with PD have lower vitamin D levels then healthy individuals and persons with Alzheimer's.[5] Vitamin D may be particularly low in persons with PD in the Northwest. A study looking at medical residents at OHSU found that in the spring 47% had deficient levels.[6] The recent attention vitamin D has received in the medical and lay press may in contrast increase levels, with participants possibly already be on supplementation.

Preliminary Data

Vitamin D in Men with Osteoporosis: Dr. Peterson presented a poster at a national meeting regarding vitamin D levels in men with and without PD. The data was obtained from a large cohort study, The Osteoporotic Fractures in Men (MrOS) study. Vitamin D levels were lower in men with PD compared to controls; 22.8 (±6.7) ng/ml vs. 24.4 (±7.9) ng/ml; but this difference was not statistically significant.

Vitamin D and Osteoporosis Assessments in Veterans with PD**:** Dr. Peterson has an abstract accepted for the 2009 Movement Disorder's Society meeting entitled "Vitamin D and bone density assessments are rarely obtained in veterans with Parkinson's disease (PD)." Out of a total of 3,128 persons carrying a diagnosis of Parkinson's disease only 236 or 7.5% had a vitamin D level checked, during the five year period assessed. Even fewer, 129 or 4.1%, had bone density testing. The data shows that osteoporosis and its risk factors in Parkinson's patients are vastly under assessed within the VA system, despite the increased risk of falls in this patient population.

Sensory Organization Test (SOT): Figure one shows results for one of the balance measure, the SOT, for a completed study subjects. There are six scenarios. In scenarios 1-3 the surface is fixed with eyes open for 1, then closed for 2, and then with movement of the surround for 3 (see figure 2). In scenarios 4-6 the base the subject is standing on moves in response to their movements, termed sway-reference. In 4 the eyes are open, in 5 the eyes are closed, and in 6 the surround area moves. Scores on SOT have been shown to correlate to falls.

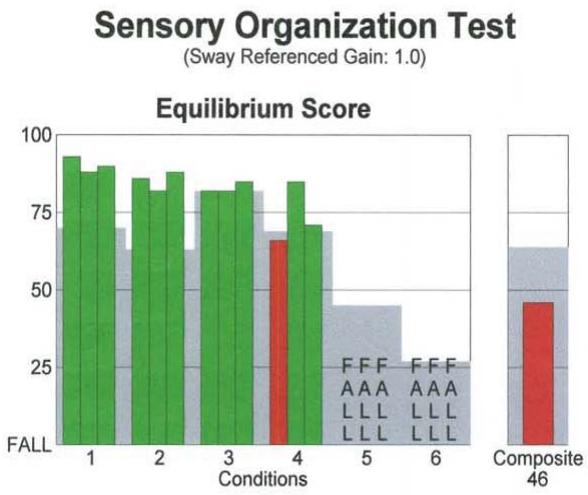

Figure 1: Sample SOT

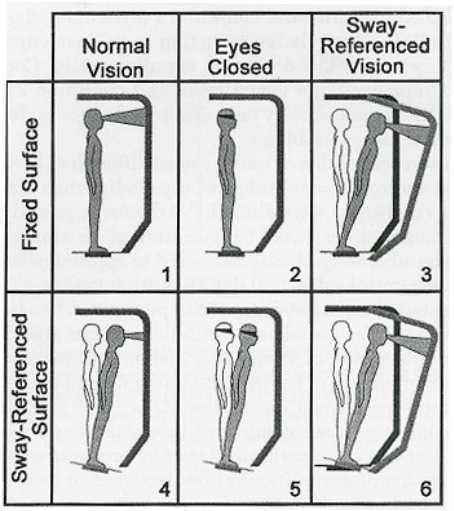

Figure 2: SOT conditions

Study Design

This is a pilot study. We will recruit 40 subjects with idiopathic PD to measure balance and vitamin D levels in preparation for an intervention study. To determine if we can measure balance deficits, using clinical posturography all subjects will undergo a battery of computerized balance testing. Specific results from these measures will be compared to the vitamin D levels to look for a relationship between balance and vitamin D in Parkinson's subjects. Falls in the month proceeding the testing will also be analyzed for a relationship with the balance measures. Finally the relationship between fall rates and Vitamin D will be examined.

Study Population

Inclusion Criteria: 1. Medically confirmed diagnosis of Parkinson's disease by a movement disorders specialist using the National Institute of Neurological disorders and Stroke (NINDS) criteria. 2. Ability to ambulate 50 feet without the assistance of another person. 3. Ability to cooperate with balance and cognitive testing. 4. Greater than or equal to 21 years of age.
Exclusion Criteria: 1. Significant cognitive deficits as defined by a Mini Mental Status Exam (MMSE) of <25. 2. Another neurological or orthopedic deficit that in the investigator's opinion would have a significant impact on gait and cognition (e.g. stroke, fracture).
Plans for recruitment:: Potential subjects will be identified through the movement disorders clinic at OHSU and the Portland VA. Flyers will also be hung at OHSU and the VA.

Study Procedures

Balance Measures: Assessments will occur approximately half way between Parkinson's disease medication doses for those on medications or at any time for those who are not medicated. The PI, Amie Peterson, or a trained physical therapist will perform the studies. The testing will take place on the 8th Floor in Rehab Services in the main hospital. The following subset of all the balance tests available has been selected based on likelihood that they will be sensitive to balance deficits in PD.

Dynamic Posturography Platform:

Sensory Organization Test (SOT): The SOT quantifies abnormalities in the three sensory systems that contribute to postural control (somatosensory, visual and vestibular) as well as the brain's central integration of these. This test produces an overall composite score which will be used in the analysis.
Backwards Translations: Measures latency, symmetry, amplitude scaling, strength, and symmetry on to backward movement.. This test produces a single composite score from the 4 measures of latency which will be used in the analysis.
Unilateral Stance Eyes Open and Closed: This test quantifies mean sway velocity and symmetry of standing on one leg with eyes open and closed. The higher sway velocity (right or left) with eyes closed and eyes opened will be used in the analysis.

Long Force Plate Testing:

Sit to stand: Measure the time to move center of gravity (COG) over the feet, the amount of force exerted by the legs during the rise phase, sway velocity (COG sway) and weight symmetry both during the sit to stand and for 5 seconds after. The COG sway velocity will be used in the analysis.
Walk and turn: Measures the turn time (amount of time to complete 180 degree turn) and turn time difference (compares left and right turns), turn sway and turn sway difference. The slower turn time and higher turn sway (right or left) will be used in the analysis.
Falls assessment: Will be asked how often they have fallen in the last month.
Vitamin D Levels: Approximately 3 ml of blood will be drawn by OCTRI staff and frozen and stored until the conclusion of the study. 25-hydroxyvitamin D (25-OHD) will be checked on serum samples at the conclusion of the study. Subjects will be contacted at the end of the study by phone and notified of their vitamin D levels. If it is less 30ng/ml they will be told this is considered low and it will be suggested that they follow up with their primary care doctor for management.

Cognitive battery: 1. Mini Mental Status (MMSE) Examination, 2.Trail Making Test parts A and B, 3. Verbal fluency (naming as many animals as able in 1 minute), 4. Clock draw.
Motor function: Unified Parkinson's Disease Rating Scale (UPDRS) motor score .
Medication list: Subject will be asked about their prescription and over-the-counter supplements and medications.
Dyskinesia Assessment: Modified Abnormal Involuntary Movement Scale (AIMS)
Physical Activity Score: This will be quantified using the Physical Activity for the Elderly (PASE). This is a paper questionnaire and will take 5-15 minutes to complete.

Timetable and organizational chart

Prior to study visit	Recruitment		
Study Visit (80 minutes)	**Consent** (5 minutes)	**Possible Confounders:** (30 minutes) • Knowing, thinking, and learning tests • Parkinson's assessment • Medication list • Modified Aims	**Measures:** (45 minutes) • Falls Assessment • PASE assessment • Balance measures • Blood Draw (1 tsp)
After Completion of Study	Contact subjects with vitamin D level		

Statistical Analysis
Specific aim 1: Linear regression analyses will be performed comparing vitamin D levels to each of 7 measures from the dynamic posturography testing (see the methods section for the specific measures to be used in the analysis). These results will also be adjusted for disease severity as measured by the UPDRS motor score. A linear regression will be performed comparing vitamin D levels for those with no falls in the prior month to those with one or more falls. The results will be adjusted again for disease severity as well as for physical activity with the physical activity score. The final comparisons will be linear regressions comparing dynamic posturography measures between those with and without falls in the previous month, again with adjustments for disease severity and physical activity. Primary analyses above adjust for the most critical confounders; secondary analyses for each comparison will incorporate additional potential confounders: medication that may worsen balance, muscle strength, and cognition (one at a time) to assess their impact on the above relationships.

Specific aim 2: To determine the prevalence of vitamin D deficiency in subjects with PD, the levels will be measured and the percent of subjects with deficient (<20ng/ml), insufficient (≥20ng/ml - < 30ng/ml), and sufficient (≥30ng/ml) vitamin D 3 levels will be calculated. 95% confidence intervals for the percentages of subjects in each Vitamin D category will be obtained. Secondary analysis will incorporate the season of the blood draw and vitamin D supplementation to allow evaluation based on these factors as well.

Power calculations: To detect a difference of 3 ng/ml in vitamin D levels between fallers and nonfallers (assuming 50% are fallers) with 80% power 36 subjects would be needed, 80% power for a difference of 4ng./ml would require just 22 subjects (see table 1). All power calculations

are using an alpha of 0.05. Considering that 10ng/ml is the division between sufficiency categories for bone health this would allow for a much lower difference to be detected. If there is a difference in one standard deviation of the dynamic posturography measures in the fallers and nonfallers this would be detected with 32 subjects with 80% power. (see table 2) Based on these numbers, a sample size of 40 subjects is reasonable to detect as low as 3 ng/l difference in vitamin D levels and 1 standard deviation in dynamic posturography; both values that seem appropriate as a meaningful difference. The association between posturography measures and vitamin D levels is based on regression/correlation analysis. A sample size of 40 provides 80% power to detect a correlation of 0.43 or higher. With a sample of size 40 in this pilot study we will also be able to obtain reasonable descriptive information on all measures in order to plan a larger (confirmatory) study.

Table 1: Vitamin D Levels

Power	Alpha	Difference in Vit D levels	Sample size
0.8	0.05	5	14 (7,7)
0.8	0.05	4	22 (11,11)
0.8	0.05	3	36(18,18)

Based on Vitamin D of 8.9 ($\pm$3.2) ng/ml

Table 2: Dynamic Posturography Measures

Power	Alpha	Difference in COG Sway Velocity	Sample size
0.7	0.05	1 SD	26 (13,13)
0.8	0.05	1 SD	32 (16,16)
0.9	0.05	1 SD	44(22,22)

Resources and Environment

The office and computer resources at both OHSU and the VA are adequate for Dr. Peterson to complete the proposed research. Clinical space is available through the Oregon Clinical and Translational Research Institute (OCTRI) which is located on the OHSU campus, in a building connected to the main hospital. It is equipped with 10 self-contained clinic rooms that can be used for subject consent, examination, and testing. The equipment for the clinical posturography is located near the OCTRI, on the 8th floor of the main hospital, within the physical therapy department. It is one of only three research level clinical posturography systems in the world, including additional force plates, ability for new testing programs to be developed in addition to the standard battery, and raw data can be looked at in more detail. The expanded capacity is crucial in gaining greater insight in the mechanism by which vitamin D effects balance.

Human Subjects

Potential Risks

There is minimal risk involved in the proposed research. The blood draw may result in slight pain, bleeding, bruising, or infection. To decrease the likelihood of such complications, all blood draws will be performed by trained phlebotomist. There is a risk that subjects may fall when taking the balance tests. To reduce this risk, subjects will be placed in a safety harness for the tests with the moveable platform. This is a device that wraps around the subjects' shoulders, waist, and legs, and is attached at the shoulders to the equipment. In addition, a technician will stand within arm's length of the subject during the testing and will brace the subject if needed. To protect confidentiality, each subject will be identified with a unique numerical identifier, which will be used for all testing. The data will be kept in a locked file cabinet in a locked office when not being used. Banked blood will be labeled with a unique numerical identifier and will be kept in a secure lab.

Potential Benefit of Proposed Research to Human Subject and Others

All subjects participating will be informed of their vitamin D level at the completion of the study. Vitamin D deficiency and insufficiency often goes unrecognized. On a recent review of VISN20 data less than 8% of persons with PD had ever had a vitamin D level checked. The information obtained, seeing if vitamin D improves balance in PD, is important for the subjects involved. Most persons with PD experience balance difficulties at some point in time and the more data that is known the better their management will be when that time comes. It is also possible that an individual subjects testing will reveal a balance disorder of a different etiology that could result in additional treatment and improvement.

Recruitment and Informed Consent

Subjects will be recruited at the Portland Veterans Affairs (VA) Hospital and OHSU movement disorders clinics. The Parkinson's Disease Research, Education & Clinical Center (PADRECC) at the Portland VA and the Parkinson's Center of Oregon (PCO) at OHSU, both have good records of recruiting and enrolling PD patients in research protocols. The PADRECC and PCO saw 480 and 585 patients with PD respectively in the last year; this does not include additional research subjects who are not seen clinically. A recent study on falls recruited 105 patients over an 18 month period. Potential subjects will also be recruited through flyers that will be posted in patient waiting areas in the VA and OHSU.

Dr. Peterson will obtain informed consent, informing persons who meet subject criteria about the details of the study and will invite them to sign a consent form before participating. Potential subjects will be told that their participation or lack of participation will not affect the clinical care they receive.

Literature Cited:

[1]Wood, B. H., Bilclough, J. A., Bowron, A., & Walker, R. W. (2002). Incidence and prediction of falls in Parkinson's disease: A prospective multidisciplinary study. *Journal of Neurology, Neurosurgery & Psychiatry, 72*(6), 721-725.

[2] Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, Wong JB. Effect of vitamin D on falls: A meta-analysis.[see comment]. JAMA 2004 Apr 28;291(16):1999-2006.

[3]Pfeifer, M., Begerow, B., Minne, H. W., Abrams, C., Nachtigall, D., & Hansen, C. (2000). Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. *Journal of Bone & Mineral Research, 15*(6), 1113-1118.

[4]Eyles, D. W., Smith, S., Kinobe, R., Hewison, M., & McGrath, J. J. (2005). Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. *Journal of chemical neuroanatomy, 29*(1), 21-30.

[5] 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 Oct;65(10):1348-52.

[6] Haney, E. M., Stadler, D., & Bliziotes, M. M. (2005). Vitamin D insufficiency in internal medicine residents. *Calcified Tissue International*, 76(1), 11-16.