Vitamin D Supplementation on Physical and Cognitive Function-Pilot Study

PI: James B. Post, MD

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PART II
RESEARCH PROPOSAL

A) SPECIFIC AIMS.

Current practice guidelines from the National Kidney Foundation (NKF) do not require monitoring for or correction of 25-OH vitamin D deficiency. Instead, the guidelines for vitamin D therapy in hemodialysis (HD) patients recommend using active (1-25 OH) vitamin D to suppress serum parathyroid hormone (PTH) levels to a recommended range of 150-300 pg/ml. The current NKF guidelines for vitamin D therapy in HD patients focus on narrowly maintaining biomarkers of skeletal health and fail to address the important functions of vitamin D on extra-skeletal tissue. Despite the current vitamin D regimen recommended by the NKF, HD patients have a very high prevalence of 25-OH vitamin D deficiency. At the same time, HD patients experience muscle weakness, muscle fatigue, and cognitive impairment all of which have been associated with 25-OH vitamin D deficiency in the general population. Our broad long-term objective is to improve muscular strength, postural balance, muscular performance, and cognition by supplementing HD patients with vitamin D deficiency (<20 ng/ml). Our goals in this pilot study are to 1) assess the feasibility of recruiting and retaining HD patients in this study, 2) evaluate the proposed regimen for safely increasing 25-OH vitamin D levels with oral supplementation 3) develop the knowledge and experience with critical outcome measures for a future pivotal trial to assess the benefits of vitamin D supplementation on function and cognition in the HD population. We will accomplish this through a feasibility study with the PRIMARY objective to determine the effect of vitamin D supplementation on neuromuscular and cognitive functioning in HD patients by performing a feasibility study. Our hypothesis is that muscle strength, muscle performance, postural balance, and cognitive function will improve after vitamin D has been supplemented into the normal range (≥30 ng/ml).

In patients with chronic kidney disease who are on HD, we propose to perform a 6 month randomized, double blind, placebo-controlled trial to determine the feasibility of the following specific aims (SA):

SA1: To compare functional performance benefit between HD participants randomized to vitamin D supplementation and placebo. Function will be measured by the 50ft timed walk, the Timed Up and Go test (TUG), a timed stair climb, the Chair Raise test, the Functional Reach test, postural sway, and muscle handgrip, hip flexor and knee extensor strength.
H1: We hypothesize that a greater proportion of the subjects will demonstrate an improvement in postural sway in the treatment group than in the placebo group.
SA2: To compare cognitive function as measured by neuropsychological testing between HD participants randomized to vitamin D supplementation and placebo.
H2: We hypothesize that a greater proportion of the subjects will demonstrate an improvement in the treatment group than in the placebo group.
SA3: To compare the Self-report of physical activity and quality of life (QOL) between HD participants randomized to vitamin D supplementation and placebo.
H3: We hypothesize that the total score on the Physical Activity Scale for Persons with Physical Disabilities (PASIPD) and the QOL scores will significantly improve in the treatment groups versus no change in the control group.
SA4: To compare immune function between HD participants randomized to vitamin D supplementation and placebo.

H4: We hypothesize that immune function will be increased in the treatment group versus no change in the control group.

B) BRIEF REVIEW OF RESULTS OF OTHERS AND CURRENT STATE OF KNOWLEDGE

Pathophysiology and Management of Vitamin D and Deficiency in HD Patients:

Patients receiving hemodialysis (HD) have a decreased capacity to convert nutritional vitamin D (25-OH) to the active form of vitamin D (1-25 OH). This occurs because the kidney is the major endocrine organ for activating vitamin D through the 1-alpha hydroxylase enzyme system. As the kidney reaches end-stage disease, such as in those patients on HD, this enzyme produces insufficient levels of active vitamin D that are required to maintain parathyroid hormone (PTH) within physiologic range. Out-of-control elevation of PTH is associated with significant bone loss and increased mortality in HD patients. As a result, the NKF guidelines for the management of vitamin D therapy in HD patients recommend administering intravenous 1,25 (OH) vitamin D intermittently to HD patients in order to control the PTH level (1). Despite this intervention, several reports have documented a high prevalence of 25-(OH) vitamin D deficiency in HD patients (2, 3). Current NKF guidelines do not require monitoring for adequate nutritional or 25-(OH) vitamin D levels based on reasoning that reduced 1-alpha hydroxylase activity in the failed kidney cannot convert 25-OH vitamin D substrate to sufficient levels of active vitamin D that are needed to suppress PTH. However, it has been increasingly appreciated that vitamin D has important actions on several extra-skeletal tissues and 1-alpha hydroxylase is widely present in tissues other than the kidney. Since the current IV administration of active vitamin D (1-25 OH) to HD patients does not correct 25-OH vitamin D levels, several extra-skeletal tissues such as muscle and nerve are likely deprived of the essential substrate needed to produce local active vitamin D for cellular functions. By relying entirely on biochemical endpoints of bone disease (PTH) to determine vitamin D therapy in HD patients, we are likely neglecting the full spectrum of clinical conditions that have been shown to be associated with 25-OH vitamin D deficiency.

Actions of vitamin D on extra-skeletal tissue and role of extra-renal 1-alpha hydroxylase:

The “classic” role of vitamin D includes the regulation of blood calcium and phosphate concentrations by actions on the intestine, bone, parathyroid gland and kidney. These classic physiologic actions have been known since the early 1900’s when dietary vitamin D deficiency was first demonstrated. More recently, autoradiographic studies using radiolabeled active vitamin D or calcitriol, vitamin D receptor (VDR) protein distribution studies, and data from various gene knockout mice, show that vitamin D, in the active form acts upon a wide variety of cells in the body (4). Vitamin D is a hormonal system involved in the regulation of nearly 800 genes not simply limited to genes that regulate calcium and phosphate transporters (5). The vitamin D-dependent genes have several “nonclassical” physiologic functions which include cell differentiation and anti-proliferative effects on the immune system, skin, prostate epithelial cells, and muscle tissue. In muscle tissue, VDRs have been identified in the nucleus and cell membrane (6). At the genomic level, $1,25(OH)_2D$ binds to a nuclear receptor forming a complex that then binds to vitamin D response elements to regulate gene expression of messenger RNA and subsequently protein synthesis (7). This genomic pathway was found to influence muscle cell calcium uptake, calcium transport across the cell membrane, and mediate cell proliferation and differentiation into mature muscle fibers (8-11). At the non-genomic level, vitamin D has rapid effects mediated by the cell membrane VDR, which results in second messenger signaling or phosphorylation of intracellular proteins (12). These actions have been shown to result in calcium release which is essential for muscle contraction. The specific allelic variant of the VDR also affects the response to vitamin D metabolites. With restriction endonucleases several VDR polymorphisms have

been identified. Muscle strength appears to be influence by the genomic type of VDR in the muscle cell (13). Muscle biopsies from adults with vitamin D deficiency show type II muscle fiber atrophy which are the first fibers to be recruited to maintain posture and prevent falling (14). Additionally vitamin D supplementation has been shown to increase type II muscle fiber diameter with long-term supplementation (15). The nuclear receptor for vitamin D has been identified in areas of the brain known to regulate behavior such as the cortex, cerebellum and limbic system, where it is often co-localized with 1-alpha hydroxylase (16). In animal studies, active vitamin D stimulates neurogenesis and regulates the synthesis of neurotrophic factors which are important for cellular differentiation and survival (17). HD patients currently receive intermittent active vitamin D supplementation to replace the deficiency secondary to failing 1-alpha hydroxylase in the kidney and to suppress rising PTH levels. Given the short biological half-life of active vitamin D analogs and the intermittent dosing schedule, HD patients are not likely to achieve vitamin D levels that will support its multiple functions in various body tissues.

Although the production of vitamin D by the kidney to regulate calcium-bone homeostasis is severely impaired in HD patients, autocrine vitamin D is produced in several tissues by extra-renal 1-alpha hydroxylase (4). Approximately 80% of vitamin D utilization daily is through the autocrine mechanism where it is believed to augment circulating vitamin D with local production (18). Intracellular production of active vitamin D may give rise to altered patterns of gene expression, which may limit cell growth and lead to tissue specific differentiation of specific cell types (4). The extra-renal production of active vitamin D is dependent on adequate serum levels of its precursor, 25-OH vitamin D (5). Adequate serum 25-OH concentrations increase intracellular specific, 1-alpha hydroxylases, thereby increasing intracellular concentrations of $1,25(OH)_2D$ in muscle and other tissues (19). Additionally, circulating 25-OH vitamin D levels have been shown to correlate well with a number of clinical factors particularly in the health and function of the immune system, skin, bone and muscle (20). Thus, in appreciation of the increasing physiologic role of extra-renal 1-alpha hydroxylase, the current narrow clinical practice of the administration of active vitamin D to merely meet calcium bone metabolism endpoints may not constitute adequate vitamin D supplementation in HD patients.

<u>The effect of 25-OH vitamin D on muscular function and cognition:</u>

Cross-sectional studies have found a direct association between 25-OH levels and lower extremity function. Functional assessments have included the 8-foot walk test and sit to stand test that were performed in 4100 ambulatory older adults in NHANES III (21). For both tests, performance speed increased throughout the range of 25-OH vitamin D with most of the improvement noted at concentrations from 9 to16 ng/ml. Additional improvement in function was observed in the range from 16 to 38 ng/ml; however the effect was less impressive. Individuals in the highest quintile of 25- OH performed significantly better on the 8-foot walk and sit to stand and those in the lowest quintile. Similar findings were noted in the Longitudinal Study of Aging Amsterdam (LASA) that included 1351 individuals $\geq$ 65 years old (22). In this cross-sectional study, a composite physical performance score showed greatest improvement from very low 25-OH levels to20 ng/ml. In a prospective 3-year follow-up of the LASA study, individuals with a 25-OH level < 20 nmol/l were found to be at an increased risk of decline in physical performance compared to those with levels $\geq$ 30 ng/ml (23). Therefore, these cross-sectional studies suggest that 25-OH levels > 16 ng/ml are desirable for muscle performance and that conceivably increasing levels to 40 nmol/l may provide additional benefit. Randomized clinical trials have examined the effect of vitamin D supplementation on tests of physical performance in muscle strength. Vitamin D supplementation with calcium, compared to calcium alone was shown to improve body sway by 9% in subjects with serum 25- OH levels less than 20 nm/l within 8 weeks of treatment

(24). In a 20 month trial, vitamin D supplementation with calcium, versus calcium alone significantly improved body sway by 28% and decreased the time needed to perform time up and go test by 11% in those with 25-(OH) vitamin D levels < 31 ng/ml (25). In another randomized controlled clinical trial patients received 6 months of calcium and vitamin D (150,000 units/month for the first two months, followed by 90,000 units/month for the last 4 months) or calcium and placebo to determine the effect on lower limb muscle strength (26). At 6 months, the group on placebo showed no change in knee extensor or hip flexor strength while the group on vitamin D arm showed a significant increase in hip flexor of 16% and a significant increase of 24% in knee extensor strength. Further studies are required to determine the optimal dose of 25-(OH) vitamin D to attain optimal muscle performance and strength.

Recent studies have begun to evaluate the role of 25–OH vitamin D levels on cognitive function. In a retrospective review of 80 elderly patients, a significant positive correlation was observed between serum 25-OH levels and performance on the mini mental state examination (27). In a larger cross-sectional study of 1766 adults > 65 years old, individuals in the lowest 25-OH quintile were twice as likely to have cognitive impairment versus those in the highest quintile using the Abbreviated Mental Test Score (28). Results from comprehensive neuropsychological testing suggest that vitamin D deficiency may have a deleterious effect on subcortical cognitive function. In a study of 703 individuals > 65 years old, significant correlations were found between the 25-OH level and measures of executive function and attention/processing speed (29). In this study, 25-OH levels were associated with significantly better performance on Trails A, Trails B, digit symbol, block design, and digit span tests. There was no association between 25-OH level and any measures of memory. These recent findings are in agreement with another cross-sectional study which showed that vitamin D deficiency was associated with poor performance on the short blessed test which is a measure of the central processing speed (30). Currently, the threshold serum level of 25-OH for optimum cognition is not known except for a single study that demonstrated a relationship between serum vitamin D and cognitive function with function most impaired at concentrations below 15 ng/mL (31). The role of vitamin D supplementation in improving cognition has not been studied.

<u>Role for 25-(OH) vitamin D supplementation in HD patients:</u>

The most rapid growing segment of the HD population is those older than 75 years, and the prevalence of 25-OH vitamin D deficiency in this group has been recorded to be as high as 90% (2, 32). HD patients frequently experience muscle weakness, fatigue, and impaired cognition which is likely a significant contributor to morbidity. (33-36).

Muscle weakness is a well recognized, but poorly understood, phenomenon in patients who are receiving HD. In a study of chronic HD patients, cross-sectional area of the contractile tissue in the lower leg showed significant atrophy compared to controls and muscle atrophy was associated with poor muscular performance (37). In another study of 49 HD patients, proximal muscle weakness and abnormal muscular relaxation were associated with a poor nutritional state (34). In this study, 40% of patients showed atrophy of type II muscle fibers and type b fibers were smaller than that of controls. Complex muscle physiology studies have shown that the mechanisms underlying excessive muscle fatigue in chronic HD patients likely include both intramuscular energy metabolism and failure of central activation (35). Another potential mechanism for poor muscle performance in chronic HD patients may involve impaired muscular excitation-contraction coupling abnormalities (38). This mechanism is based on evidence that a marked reduction in all parameters of calcium ion transport by the sarcoplasmic reticulum reversed after administration of $1,25(OH)_2D_3$ (39, 40). These findings suggest that excitation-contraction coupling is abnormal in dialysis patients because calcium release from the sarcoplasmic reticulum is required in the sequence of events leading from excitation to

contraction. The threshold 25-OH vitamin D level at which muscular function is optimal in HD patients has not been discussed. Additionally, the effect of correcting vitamin D deficiency on muscular function in the HD population has not been evaluated. Because of the emerging literature that has found improvement in functional status in the elderly after vitamin D supplementation and the high prevalence and severity of vitamin D deficiency in the HD population, improved muscle function following vitamin D supplementation in this population is extremely plausible.

The high prevalence of cognitive impairment among HD patients is likely multifactorial. However, early signs of impairment prior to the development of dementia may offer an opportunity for intervention. In two cross-sectional studies, cognitive impairment, defined by a Mini-Mental State Examination (MMSE) score of < 24 was present in 32% to 60% of HD patients (41, 42). More recent studies have reported normal cognitive function in only 12% of HD patients with 38% of all patients showing severe deficit in the domain of executive function (33, 43). Prior to the development of dementia, HD patients with MMSE > 24 show early signs of cognitive deficits in sub-cortical domains with relative sparing of cortical function including the memory domain (44). These recent studies suggest that HD patients have a very high prevalence of dementia and a potential prodrome of mild cognitive impairment in the domains of executive function. The effect of correcting severe vitamin D deficiency on cognitive function this population has not been studied.

Given the safety, low cost of supplementation, and potential clinical benefits, we are proposing a study to evaluate the effect of vitamin D supplementation on neuromuscular and cognitive function in HD patients. Poor muscle strength and impaired are potential clinical markers for falls which are highly prevalent in the HD population. Improving cognition and muscular strength using a safe and inexpensive intervention could potentially result in improved compliance with medical care and independence as well as reduce the rate of falls which is associated with high cost, morbidity, and potential mortality.

Dosing of 25-OH vitamin D in HD Patients:

The current standard of care involves the administration of active 1-25 OH vitamin D intravenously during dialysis. The dose is determined by the patient's private nephrologist based on monthly laboratory reports. Because 25-OH vitamin D supplementation is not currently recommended in HD patients, only a limited number of studies have examined the efficacy and safety of cholecalciferol and ergocalciferol vitamin D replacement in this population. Currently two studies have evaluated the safety and efficacy of 25-OH replacement in HD patients over a 6 month duration. In one study, oral 25- OH vitamin D was given daily in doses ranging from 400 units to 1200 units based on severity of vitamin D deficiency (45). All patients had 25-OH vitamin D levels < 30-ng/mL and 87% achieved levels > 30 ng/mL without evidence of toxicity. In another study in which 52% of patients had 25-OH < 15 ng/ml and 92% had levels < 30 ng/mL; after 6 months of treatment using 50,000 U of ergocalciferol, 94% of patients had 25-OH levels > 30 ng/mL and none were < 15 ng/mL (2). The treatment was well tolerated without evidence of toxicity. The safety of cholecalciferol administration to HD patients was demonstrated after 100,000 units of cholecalciferol were given monthly for 15 months; vitamin D deficiency was corrected in nearly 90% of patients (46). Using more frequent doses of vitamin D, 20,000 units of cholecalciferol were given weekly to HD patients with levels < 15 ng/mL for 9 months and followed up with maintenance dosing at 20,000 per month for 15 months; vitamin D was well tolerated and without adverse effects, however only 57% of patients achieved levels > 30 ng/mL which is considered optimal (47). Given the safety of these studies, we propose administering 50,000 units of cholecalciferol every week with level monitored monthly to insure response to treatment and to adjust dose if levels raise > 60 ng/mL. Patients in both arms of the study will receive the current standard of

care of receiving active 1-25 OH vitamin D during dialysis. However, our objective is to supplement deficient 25-OH vitamin D levels with cholecalciferol (not active vitamin D, but substrate) which is currently not standard of care. Vitamin D supplementation will be administered in the unit by research staff to insure compliance. Administration of 50,000 units of cholecalciferol twice a month is the recommended dose to maintain 25-OH levels between 30 and 40 ng/mL in patients with advanced renal disease not yet receiving hemodialysis.

The management of secondary hyperparathyroidism of end-stage renal disease will be managed by the patient's nephrologists according to the NKF KDOQI guidelines. Active vitamin D analogs and a combination of calcium and/or non-calcium containing oral phosphate binders will be administered and titrated based on monthly routine dialysis laboratory tests in order to meet the recommended KDOQI targets for intact PTH, calcium level, and phosphorus level. In previous studies, administration of oral 25-OH vitamin D has not shown significant clinical effect on serum phosphorus or calcium levels.

The 25-OH vitamin D levels will be measured monthly and pre-dialysis blood-work will be evaluated monthly as part of routine clinical practice for serum calcium, albumin, phosphorus, and intact PTH. All patients will be receiving 3 hemodialysis sessions per week, 3 to 4 hours session based on achieved clearances, and standard calcium bath concentration of 1.5 mmol/L will be used.

C) PROCEDURES, METHODS AND EXPERIMENTAL DESIGN.

If this study involves human subjects, or biologic materials obtained from humans, sufficient information must be provided to weigh the risk against the benefits. The "Procedures" Section (IIC) should contain a detailed description of experimental design, methods and procedures.

Research Design and Methods:

We propose to perform a prospective, randomized, double-blind placebo controlled trial. Patients will be included if they are: 1) receiving outpatient hemodialysis at the James J. Peters VAMC, 2) receiving IV vitamin D therapy according to National Kidney Foundation guidelines, 3) between the ages of 45-89 years, 4) a veteran outpatient or stable community living center patient, and 5) able to ambulate independently or with an assistive device for at least 20 feet. Exclusion criteria include: 1) 25-OH vitamin D level $\geq$ 25 ng/ml, 2) hypercalcemia, 3) active malignancy within 6 months, 4) receiving intravenous antibiotics for infection, 5) history of dementia, 6) hemoglobin < 8.5g, 7) history of conditions that interfere with postural instability (e.g. cerebellar disease, vestibular disease or any others that may present), and 8) poor compliance with dialysis treatments (history of skipping $\geq$ 2 treatments per month for > 2 months). A 25-OH vitamin D level of < 25 ng/ml level was chosen based on previous studies that have shown that patients have the greatest improvement in muscle strength when levels below this threshold are increased. Patients will first be identified based on the inclusion criteria, then informed about the study and consented. Those who meet the exclusion criteria will be randomized to treatment or placebo. Enrolled participants will be randomized 2:1 to receive vitamin D (n=20) or placebo (n=10) for 6 months. All participants will be tested twice over two weeks to establish baseline values. Following baseline testing, the treatment group will receive 50,000 IU (standard replacement therapy) of oral cholecalciferol or placebo. The initial dose of cholecalciferol will be 50,000 IU weekly for 6 weeks. Vitamin D levels will then be measured. Participants who still have Vitamin D insufficiency ($\leq$ 35 ng/ml) will remain on 50,000 IU of cholecalciferol for another 6 weeks, at which point Vitamin D levels will be measured again. Participants who reach 25-OH levels > 35 ng/ml will have their dosing regimen lessened to 10,000 IU weekly (maintenance dose) for the remainder of the 6 months. Participants receiving placebo will start taking the placebo maintenance dose after the first 6 weeks. For safety monitoring, 25(OH) vitamin D_3 levels will also be re-measured at monthly intervals and followed by an independent medical monitor. In patients who have serum vitamin D levels $\geq$ 60

ng/ml, the frequency of administration will be reduced to once a month. The participants will receive supplementation for a total of 6 months. At this time, vitamin D levels will be reassessed and participants will undergo follow-up functional assessments, and cognitive and immune testing. Subjects will be recruited from the outpatient hemodialysis (HD) unit which is located on the fourth floor of the James J. Peters VAMC.

Primary Outcomes (tested at Baseline, 3 months and 6 months):

1) Neuromuscular functional performance using the 50ft timed walk, the TUG, a timed stair climb, and the Chair Raise test, (48)
2) Postural stability using a Sway meter (NeuroCom International, Inc., Clackamas, OR) that measures displacement of the body at the level of the waist in 30 second periods (49) and the Functional Reach test.
3) Muscle hand grip strength using the Harpenden Hand Grip dynamometer (50) and hip flexor and knee extensor strength using a Push-Pull Muscle Strength dynamometer.

Secondary Outcomes:

1) Cognitive function (tested at Baseline, 3 and 6 months):
   a) Mental Status: Mini-Mental Status Exam (MMSE) (51) and Short Blessed Test (SBT) (52);
   b) Memory: California Verbal Learning Test – II (CVLT-II) (53);
   c) Language: Category Fluency and Controlled Oral Word Association Test (COWAT) (54);
   d) Attention and Processing Speed: Trails A (55), Digit Span (56), Symbol Digit Modality Test (SDMT) (57), and Stroop Color and Word (58)
   e) Executive Function: Trails B (55) and Stroop Color-Word (58).
2) Self-assessment of Physical Fxn and Health (tested at Baseline, 3 months and 6 months):
   a) Physical Activity Scale for Persons with Physical Disabilities (PASIPD) (59)
   b) NIH PROMIS (v1.0 Item Banks): Global Health Physical Function, Pain, Fatigue, Sleep, Emotional Distress (60)
   c) Beck Depression Inventory (BDI)
3) Immunology (tested at Baseline, 6 months)
   a) Serum cytokines

This study will be performed over two years.

TABLE 1. Study Flow Sheet	BL 1	BL 2	Month 1	6 weeks	Month 2	Month 3	Month 4	Month 5	Month 6
Week:	0	0_2	4	6	8	12	16	20	24
Physical Function Assessment									
50ft walk, TUG, stair climb, Chair Raise, Functional Reach, Sway, Hand Grip, Hip & Knee Strength		X				X			X
Self - Assessment									
PASIPD & NIH PROMIS (short forms): Physical Fxn, Pain, Fatigue, Global Health, Sleep, Emotional Distress, BDI		X				X			X
Cognitive Impairment Tests									
Mental Status: Mini-Mental Status Exam (MMSE) (for screening), Short Blessed Test (SBT)		X							X
Executive Function: Trails B, STROOP Color-Word		X							X
Memory: California Verbal Learning Test (CVLT-II)		X							X
Attention & Processing Speed: Trails A, DS WAIS-III, SDMT, StroopColor, Stroop Word		X							X
Language: Category Fluency, Controlled Oral Word Association Test		X							X
Metabolic & Endocrine Tests									
Vitamin D	X	X	X	X	X	X	X	X	X
Monthly Renal Clinic labs (chart review)		X	X		X	X	X	X	X
B12 Folate		X							X
Immune Function Tests									
serum cytokines		X							X
Demographic Data & Health Monitoring									
Age, Height, Weight, BMI, Co-morbidities, HD Hx (chart review)		X							X

Power analysis: We expect that vitamin D supplementation will improve muscular function and strength. Using information from the limited studies reported in the literature, Pfeifer, et al. (25) reported an 11% decrease in the timed up and go test for individuals treated with Vitamin D replacement therapy compared with placebo who had an average decrease. We believe our study subjects will respond in a similar manner and have powered our study such that we expect 15 of 20 subjects in the treatment group to achieve an 11% decrease in the TUG test, consistent with the Pfeifer, et. al. study findings. Similarly, postural sway has been reported by two different groups to decrease by 9% (24) and 28% (25). To be conservative, we have chosen an expected 15% decrease in postural sway in our study subjects. Muscle strength as measured by hip extensor has been reported to improve by 16% (26), and by knee extensor strength gains from 8% to 25% (25, 26). Therefore to be on the conservative side, we have

hypothesized a 10% muscle strength increase in hand grip and hip flexor strength. Only 1 of 10 in the placebo-control group is anticipated to demonstrate these improvements.

We estimate power for a two-sided test using a continuity correction. At an alpha of 0.05, with treatment response of 75% and placebo response of 10%, we estimate 90% power for a sample size of 26; 80% power with a sample size of 22 and 70% power for a sample size of 18. We are proposing a sample of 30 permitting 33% drop out to permit us to maintain reasonable power for a pilot study.

There is little information on the effect of vitamin D replacement therapy and change in cognitive function. Based on previous studies that demonstrated a correlation between poor performance and vitamin D deficiency, we expect vitamin D supplementation to improve SBT and MMSE scores (27, 30, 61). Of note, the cognitive function tests are our secondary outcome variables and we expect to gain empirical information after performing exploratory analyses regarding the effect of vitamin D replacement on cognitive function as part of this pilot study. A demonstration of improvement in neuromuscular and/or cognitive function would lead to the immediate implementation in clinical practice of 25-OH vitamin D supplementation in the care of HD patients who are vitamin D deficient and a future larger study to demonstrate dosing and length of time for maintenance of sufficient vitamin D levels to retain this positive effect.

Statistical Analysis Plan: Subjects will be randomized in a prospective, two-group, randomized study design utilizing a convenience sample of patients on hemodialysis. Subjects will be randomized to the treatment (Vit D) or placebo groups using a 2 to 1 block randomization determined from a web-based program (http://www.randomization.com). Subjects will be grouped in order of consenting such that the first 6 subjects will be in block 1, the next 6 in block 2, and so on. Five blocks will be performed. Each block will contain 6 subjects (2:1), with 4 subjects being randomized to vitamin D treatment to 2 subjects being randomized to the control group. Percent change scores will be calculated for both time points after treatment (3 or 6 month values – Baseline)/ Baseline * 100 for all primary outcome dependent variables (50ft timed walk, TUG, timed stair climb, Chair Raise, Functional Reach, postural sway, handgrip strength, and flexor/abduction strength) for each subject in both groups.

The primary analysis for functional and cognitive outcomes will use the responder analysis described above. Additional secondary analyses will be performed on the primary outcome variables. In the first analysis, the percent change variables will be used for the group comparisons and analyzed by one-way analysis of variance (ANOVA) (Y1=%change; X1=Group). The percent change variable has the advantage of being easily analyzed in an analysis of covariance (ANCOVA) model if controlling variables are identified. For example, years on hemodialysis (HD y) may be need to be controlled for and as such this model would be Y=%change; X1(HD y) + X2(Group). The second analysis to be performed on the primary outcome variables will be the more traditional two-factor mixed model (2x3 table), where the between factor is Group (treatment, placebo) and the repeated measures (i.e. the within-subjects) factor is Time (BL, 3 and 6 months). In the case of missing data we will use 2 imputation methods. First as is commonly done in clinical trials of cognitive impairment and dementia we will use the last observation carried forward for missing terminal visits. We will compare results from these methods with a variety of other imputation methods. For missing data within a specific test, we will assign the average the remaining domains for those that do not complete a domain. Other imputations will include assigning values from 1) a regression across the available time points, and 2) assigning the average value of all subjects within in the group. We will compare results using these different imputations.

Significant main effects will further be explored by single degree of freedom post hoc analyses. For the secondary analyses covariates will be used including age and education adjusted T scores will be used for the baseline versus 6 month comparisons by performing a 2x2 repeated measures ANOVA. For

the self assessment variables (PASIPD and NIH PROMIS) percent change will be calculated as previously described and analyzed by one-way ANOVA as described for the primary outcome variables above.

Immune Function Analysis Primary analysis will compare study subjects who had a 25-OH level > 35 ng/ml to study subjects who remained at a level ≤ 35 ng/ml (Vitamin D deficienct/insufficient). Potential confounders that will be examined include age, 25-OH Vitamin D level at Baseline, time on HD, sex, and ethnicity. Variables that differ significantly between treatment arms at an alpha of 0.01 and are significantly related to the immune outcomes at an alpha of 0.05 will be included in multivariable analysis. If potential confounders meet the criteria for inclusion, the multivariable analysis will be the primary analysis.

a. Basic Information (Even if described under "Procedures", list the information requested below where pertinent.)

1. What procedures will be used (i.e. biopsy, surgical operation, interview, experimental diet, infusion, drug administration, etc.) and with what frequency?

All participants will have their serum Vitamin D levels tested twice over two weeks to establish baseline values. Following baseline testing, the treatment group will receive 50,000 IU (standard replacement therapy) of oral cholecalciferol or placebo. The initial dose of cholecalciferol will be 50,000 IU weekly for 6 weeks. Vitamin D levels will then be measured. Participants who still have Vitamin D insufficiency (≤ 35 ng/ml) will remain on 50,000 IU of cholecalciferol for another 6 weeks, at which point Vitamin D levels will be measured again. Participants who reach 25-OH levels > 35 ng/ml will have their dosing regimen lessened to 10,000 IU weekly (maintenance dose) for the remainder of the 6 months. Participants receiving placebo will start taking the placebo maintenance dose after the first 6 weeks. 25(OH) vitamin D_3 levels will also be re-measured at monthly intervals and followed by an independent medical monitor. In patients who have serum vitamin D levels ≥ 60 ng/ml, the frequency of administration will be reduced to once a month. The participants will receive supplementation for a total of 6 months.

The following outcomes will be tested at **Baseline, 3 months and 6 months**:

Physical Functional assessments:

1) Neuromuscular functional performance using the 50ft timed walk, TUG test, a timed stair climb, and Chair Raise test, (48)
2) Postural stability using a Sway meter (NeuroCom International, Inc., Clackamas, OR) that measures displacement of the body at the level of the waist in 30 second periods (49) and the Functional Reach Test.
3) Muscle hand grip strength using the Harpenden Hand Grip dynamometer (50) and hip flexor and knee extensor strength using a Push-Pull Muscle Strength dynamometer.

Functional self-assessments (interview)

1) Self-assessment of Physical Fxn and Health:
   a) Physical Activity Scale for Persons with Physical Disabilities (PASIPD) (59)
   b) NIH PROMIS (v1.0 Item Banks): Global Health Physical Function, Pain, Fatigue, Sleep, Emotional Distress (60)
   c) Beck Depression Inventory (BDI)

The following outcomes will be tested at **Baseline and 6 months**:

1) Cognitive function (as conducted through participant interview):

a) Mental Status: Mini-Mental Status Exam (MMSE) (51) and Short Blessed Test (SBT) (52);
b) Memory: California Verbal Learning Test – II (CVLT-II) (53);
c) Language: Category Fluency and Controlled Oral Word Association Test (COWAT) (54);
d) Attention and Processing Speed: Trails A (55), Digit Span (56), Symbol Digit Modality Test (SDMT) (57), and Stroop Color and Word (58)
e) Executive Function: Trails B (55) and Stroop Color-Word (58).

2) Immunology (tested at Baseline, 6 months)
a) Serum cytokines

2. Provide description of these procedures. If pharmacologic agents or radioisotopes are to be administered, give dosages, mode of administration and duration of usage.

Vitamin D administration Following baseline testing, the treatment group will receive 50,000 IU (standard replacement therapy) of oral cholecalciferol or placebo. The initial dose of cholecalciferol will be 50,000 IU weekly for 6 weeks. Vitamin D levels will then be measured. Participants who still have Vitamin D insufficiency (≤ 35 ng/ml) will remain on 50,000 IU of cholecalciferol for another 6 weeks, at which point Vitamin D levels will be measured again. Participants who reach 25-OH levels > 35 ng/ml will have their dosing regimen lessened to 10,000 IU weekly (maintenance dose) for the remainder of the 6 months. Participants receiving placebo will start taking the placebo maintenance dose after the first 6 weeks. 25(OH) vitamin D_3 levels will also be re-measured at monthly intervals and followed by an independent medical monitor. In patients who have serum vitamin D levels ≥ 60 ng/ml, the frequency of administration will be reduced to once a month. The participants will receive supplementation for a total of 6 months.

Physical functional assessment tests will be conducted by a trained physical therapist. Participants will complete a 50ft timed walk, TUG test (rise from chair, walk 3m, turn back, and sit in chair), a timed 13 stair climb, and the Chair Raise test (a functional leg strength test-participants stand from chair and sit for 5 repetitions). Postural stability will be calculated as displacement of the body at the level of the waist in 30 second periods as measured by a Sway meter. The Functional Reach test has participants bend at the waist and reach out with one arm as far as they can. Muscle hand grip strength will be measured using the Harpenden Hand Grip dynamometer and hip flexor and knee extensor strength will be assessed by the Push-Pull Muscle Strength dynamometer.

Surveys (Functional self-assessment: Physical Activity Scale for Persons with Physical Disabilities (PASIPD), NIH PROMIS (short forms), and Beck Depression Inventory (BDI). Cognitive assessment battery: mini-mental status, executive function assessment, attention & processing speed assessment, memory assessment, language assessment.). The total time to perform these surveys is about 2.5 hours. *Functional self-assessment battery includes*: the PASIPD, BDI, and the NIH PROMIS short forms of Physical Function, Pain, Fatigue, Global Health, Sleep, and Emotional Distress. Functional self-assessment surveys will be performed by the research assistant. *Cognitive battery includes:* Trail Making Test A & B; Symbol Digit Modalities Test (SDMT); the Digit Span subset of the Wechsler Adult Intelligence Scale-III (DS WAIS-III), verbal memory test & delayed recall subsets of the California Verbal Learning Test-Second Edition (CVLT-II), Category Fluency, the controlled oral word association test (COWAT), and STROOP Color & Word tests. The Mini-Mental Status Exam (MMSE) and Short Blessed Test (SBT) will be performed for screening purposes only. The cognitive battery will be performed by a clinical psychologist or research assistant.

Blood draws for vitamin D and B12 Folate levels will require about 5 ml of blood for each draw. All Vitamin D levels will be determined by Quest Laboratories. B12 Folate levels will be determined by kit assay in Dr. Bauman's core laboratory as part of the CMCSCI. Vitamin D levels will be tested twice to establish baseline values. Vitamin D levels will be tested once a month during the treatment phase for safety monitoring. B12 Folate levels will be tested at baseline and 6 months. Blood draws for immune function tests will take place during dialysis sessions at baseline and 6 months. These tests will require a total of a 43cc draw. Immune function measurements include serum cytokines.

Chart review A chart review will be performed for all participants. The chart reviews will be performed by Dr. James B. Post (PI). No subject time commitment is required for the chart reviews.

3. Describe population to be studied, listing basis for selection or exclusion. Include number to be studied.
   Individuals with advanced chronic kidney disease on hemodialysis (HD) will be studied. Thirty participants will be studied: 20 in the treatment group and 10 in the placebo group. Enrolled patients will be randomized into either the treatment or placebo group.

4. If subjects are patients, will conventional therapy or diagnostic procedures be withheld or modified for the purpose of this study?
   If participants in this study are patients, conventional therapy or diagnostic procedures will not be withheld or modified. All participants will receive their normal care throughout their involvement in research.

b. List Possible RISKS

1. List possible hazards to subjects and/or investigative personnel from the procedures, drugs, or isotopes to be employed.

The main risk in this study is vitamin D toxicity. Vitamin D toxicity usually manifest first with hypercalcemia, which will be monitored by routine monthly dialysis lab tests. Moderate to severe hypercalcemia can result in symptoms of increased urinary frequency, thirst, nausea, vomiting, confusion, decreased appetite, and muscle weakness. Hypercalcemia will be first managed by adjustment of IV vitamin D (administered according to National Kidney Foundation Guidelines (NKF)) which is titrated by the patient's nephrologist and much more likely to be responsible for hypercalcemia versus oral 25-OH vitamin D. If these measures do not correct hypercalcemia, oral vitamin D supplementation will be discontinued. Efforts to correct hypercalcemia will occur as soon as the calcium levels are rise above the upper limits of normal (10.5 mg/dl) which is usually not associated with the above listed clinical symptoms.

The physical function and health questionnaires are non-invasive. The risks associated with venipuncture include: pain, bruising, swelling, and/or infection at the site of the needle puncture; and rarely fainting may also occur. There is the potential for the subject to experience some mild frustration during the cognitive impairment studies. A trained psychologist will be administering the tests.

2. Include estimates of degree of risk with documentation from recent medical literature.

We do not anticipate any patients to develop vitamin D toxicity due to our careful selection of dosing regimen that was based on previous studies. Vitamin D levels will be monitored each month along with monthly dialysis blood tests that are routinely performed on HD patients. If vitamin D levels rise above 60 ng/ml, (conservative cut off point since most reports of toxicity occur > 80 ng/ml) the frequency of

administering vitamin D will be reduced to once a month which is considered routine maintenance dosing to prevent vitamin D deficiency.

Physical function and health questionnaires, venipuncture, and cognitive assessments present minimal risk.

3. What monitoring or other safety precautions will be taken?

To protect against the any possible side effects of vitamin D supplementation toxicity, subjects' 25-OH vitamin D levels will be monitored. If a subject reaches 25-OH levels ≥ 60 ng/mL, the dose will be immediately lowered. As the PI, I will remain blinded and review monthly calcium levels to monitor for evidence of hypercalcemia. When hypercalcemia is identified, the patient's primary nephrologist will be notified so that appropriate adjustments can be made to correct hypercalcemia. The primary nephrologist's first adjustment will be to decrease the dose of IV vitamin D according NKF guidelines.

To protect against the risk of possible side effects of the blood draw, the study personnel will be trained in phlebotomy. To remove as much frustration as possible during the cognitive tests, a trained psychologist will be administering the tests.

c. Possible Benefits

Describe possible benefits from this study and state whether these benefits will be to experimental subject, to others, or both.

The benefits of vitamin D supplementation could possibly include improved muscular, cognitive, and immune function. Improvement of muscular function may allow for more patient independence on IADLs. Interventions that improve cognitive function may also lead to a healthier, more compliant HD patient. These benefits will be to experimental participants. This research also has the potential to benefit others in the future.

D) PREVIOUS WORK DONE BY YOU OR YOUR COLLABORATORS ON THIS OR RELATED PROJECTS, LISTING PUBLICATIONS.

Prevalence of Mild Cognitive Impairment in HD patients: We have collected data from 40 patients undergoing HD at the James J. Peters VAMC to determine if mild cognitive impairment exists in a healthy population with normal MMSE scores (>24) and no clinical history of stroke. Subjects were all male with a mean age of 64 ± 10y (range: 45-82y), an education level of 13 ± 2y, and 80% were non-Caucasian. All subjects underwent a comprehensive neurocognitive battery which captured the domains of memory, language, attention & processing speed, and executive function.

Results of preliminary work: Overall, mild cognitive impairment (MCI) was seen in 34 (85%) of the studied population. MCI was broken down further into amnestic and non-amnestic groupings, with 8 (20%) having amnestic MCI and 26 (65%) having non-amnestic MCI. This follows with the literature that memory is more preserved in this population compared to other domains. Of both the amnestic and non-amnestic groups, multiple domain impairment was seen more frequently than single domain impairment. (**Post JB**, Jegede AB, Morin K, Spungen AM, Langhoff E and Sano M: Cognitive Profile of Chronic Kidney Disease and Hemodialysis Patients without Dementia. *Nephron Clin Pract* 116: c247-c255, 2010)

Vitamin D deficiency in HD patients: Preliminary data of 39 of the 40 subjects show that 33 (85%) of subjects had 25-OH levels < 20 ng/ml and 6 (15%) had levels ≥ 20 ng/ml with a mean of 12.86 ± 8.03

ng/ml (range: 3.8-37.67 ng/ml). Of this convenience sample, we found a 13 point difference (based on T scores) between those with 25-OH levels < 20 ng/ml and those with levels ≥ 20 ng/ml in a test of Executive Function, trending towards significance.

E) SIGNIFICANCE OF THIS RESEARCH.

The outpatient HD unit at the James J. Peters VAMC has grown nearly 15% each year for the past two years and is one of the largest VA dialysis centers. Muscle weakness and cognitive impairment are common among HD patients and likely contributes to the high prevalence of falls in this population. Falls result in increased morbidity, decreased independence, and likely increases mortality. While cognitive impairment can contribute to falls it is also likely to result in poor compliance with complex medical treatments and medication regimens required of HD patients. Information about the possibility of improving immune function in this population could also help with quality of life. Given the safety, low cost of supplementation, and potential clinical benefits of vitamin D treatment, we propose a study to evaluate its role in improving important clinical endpoints.

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