Protocol

Protocol Title: Think-D: Can Vitamin D_3 Improve Cognitive Function in Individuals with type 2 Diabetes?
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Abstract

Diabetes increases the risk of cognitive dysfunction. The incidence of dementia is 1.5 to 2.5 times higher in persons with diabetes than the general population. There is evidence that cognitive decline significantly impacts the ability to self-manage diabetes. Strategies to prevent cognitive decline in persons with diabetes has not been well studied. A recent study reported that in persons who had vitamin D deficiency, the risk for all-cause dementia and Alzheimer's was doubled. Vitamin D receptors are located in the brain and deficiency of vitamin D has been reported to negatively affect the development of brain. Therefore, providing vitamin D supplementation to improve cognitive function is worthy of study.

We propose a small, randomized controlled trial to determine the effects of vitamin D3 supplementation in persons with type 2 diabetes who have symptoms of cognitive impairment. Participants will be randomized to receive either weekly vitamin D3 supplementation (50,000 IUs) or a matching comparator (5000 IUs) for a period of three months. The study aims are to determine (1) the effect of vitamin D3 supplementation on cognitive function and (2) the effect of vitamin D3 supplementation on diabetes self-management. A sample of persons with type 2 diabetes, who have a subjective complaint of a cognitive dysfunction or scoring at least one standard deviation below normal on a cognitive functioning screening test, have vitamin D levels less 30 ng/ml, are not depressed (as this impacts cognitive function), and do not have severe diabetes complication will be recruited. Participants will be phone screened and complete two baseline visits prior to randomization. They will then have phone call and follow-up visits to assess (1) cognitive function using standardized tests to assess for executive function (2) serum measurements (HBA1c, fasting glucose, vitamin D levels, and cardiometabolic profile) and (3) surveys to assess cognitive function as well as self-management behaviors.

Study Aims

Diabetes increases the risk of cognitive dysfunction. The incidence of dementia is 1.5 to 2.5 times higher in persons with diabetes than the general population (1). There is evidence that cognitive decline significantly impacts the ability to self-manage diabetes (2). Strategies to prevent cognitive decline in persons with diabetes has not been well

studied. A recent study reported that in persons who had vitamin D deficiency, the risk for all-cause dementia and Alzheimer's was *doubled* (3). Vitamin D receptors are located in the brain, and deficiency of vitamin D has been reported to negatively affect the development of brain and impact both growth factor signaling and neural activity (4, 5). Therefore, providing vitamin D supplementation to improve cognitive function in persons with diabetes who are at greater risk for this comorbid condition is important.

We propose a small, randomized controlled trial to determine the effects of vitamin D_3 supplementation in persons with type 2 diabetes who have symptoms of cognitive impairment. Persons will be randomized to receive either weekly vitamin D_3 supplementation (50,000 IUs) or a matching comparator (5000 IUs) for a period of three months:

Primary Aim: To determine the effect of vitamin D_3 supplementation on cognitive function for persons with type 2 diabetes.

Primary Hypothesis*:* Persons receiving weekly vitamin D_3 supplementation (50,000 IUs) will have improved cognitive function compared to those receiving the comparator (5000 IUs) at three months.

Secondary Aim: To determine the effect of vitamin D_3 supplementation on diabetes self-management.

Secondary Hypothesis: Persons receiving weekly vitamin D_3 supplementation (50,000 IUs) will have improved self-management compared to those receiving the comparator (5000 IUs) at three months.

The importance of this study is severalfold. Vitamin D supplementation is a low-cost intervention (6), it has minimal side effects (7), and it could have high impact for persons with type 2 diabetes who suffer from cognitive impairment which can significantly affect diabetes self-management.

Background and Significance

Diabetes, cognitive impairment, and self-management. Evidence indicates that diabetes is associated with cognitive impairment. In the Whitehall II cohort study, persons (n=5653) with a mean age of 54 years were followed for 10 years. It was reported that for those with known diabetes there was a 45% faster decline in memory, a 29% faster decline in reasoning, and a 24% faster decline in cognition compared to those with no diabetes (8). In the National Health and Aging Trends study (n=7606 persons), self-reported diabetes was associated with immediate and delayed word recall and poorer memory (9). Cognitive impairment makes glycemic control challenging, because self-management activities are cognitively demanding. Executive function comprises cognitive skills needed for the execution of complex activities which can include self-monitoring and daily management of diabetes. Executive dysfunction is associated with poor glycemic control (10). In a cross-sectional study of 169 patients who were

controlled with diabetes (HBA1c<7) and 104 who were inadequately controlled, it was found that any level of executive dysfunction significantly increased the odds of inadequately controlled diabetes (OR=3.6) compared to those who had the best executive functioning (11). One study (n=1200) reported the frequency of executive dysfunction among elderly diabetics was 55% (12).

Although aging is typically associated with cognitive decline, a recent report indicated that even in middle aged persons (n=1800, range 50 to 65 years of age) there was an association of type 2 diabetes and mild cognitive impairment for men (2.09) and women (1.69) (13). A recent systematic review reported that glycemia, particularly high HBA1c was associated with cognitive dysfunction, however, only 10% of the variance in cognition was explained by this factor (14). Therefore, the need to explore other factors that may contribute to cognitive impairment is needed.

Low vitamin D and cognitive impairment. A meta-analysis of 14 observational studies, 3 prospective cohort studies, and 3 intervention studies has demonstrated that lower concentrations of vitamin D was associated with executive dysfunction (especially processing speed, mental shifting, and information updating) and that repletion was associated with improved executive functioning (15). More recently, participants from the United States Cardiovascular Health Study (n=1658 adults) who were followed prospectively for six years and were found to have a doubled the risk for dementia and Alzheimers if they were vitamin D deficient at baseline (3). Persons with diabetes have been reported to have a higher incidence of vitamin D deficiency (16). Although vitamin D replacement may not directly improve glycemic control (17, 18), there is preliminary evidence to suggest that it may improve depression in persons with diabetes (19, 20). Since depression may confound cognitive function (21, 22),studying vitamin D supplementation in persons with diabetes who are not depressed is important as it would provide preliminary evidence for its benefit in preventing or improving cognitive decline.

Pilot Study

This proof of concept study examined whether vitamin D supplementation would improve diabetes symptoms and HBA1c in women with type 2 diabetes. Fifty women with type 2 diabetes (mean age 54) who were depressed (Center for Epidemiologic Studies Depression Scale, CES-D $\geq$ 16) and low vitamin D levels (<32 ng/dl) participated. A pre-post study design was used. Women were given weekly vitamin D_2 (Ergocalciferol 50,000 IUs) for a period of six months. The Diabetes Symptom Checklist, HBA1c, and vitamin D levels were collected at baseline, three, and six months. Ninety two percent of women (n=46) completed all visits. At six months following supplementation, vitamin D levels increased as expected ($p < .001$), overall diabetes symptom score improved ($p < .001$), but there was no improvement in HBA1c. Although many diabetes symptoms were alleviated following vitamin D supplementation, those that improved the most from baseline to six months were: Difficulty concentrating (35%, $p < .001$), difficulty paying attention (31%, $p = .001$), difficulty thinking clearly (30%, $p = .001$), moodiness (28%, $p = .001$), being easily irritated or annoyed (28%, $p = .002$), and overall sense of fatigue (28%, $p = .001$). These findings indicate that

improvement in diabetes symptoms is independent of glycemic regulation following vitamin D supplementation. This suggests that exploration of mechanisms to understand how vitamin D may affect cognitive functioning is needed. Furthermore, the potential to engage persons with diabetes in self-care behaviors if cognitive function improves could be a potential benefit of this cost-effective treatment.

Study Design

Design. This is a randomized, double-blind, active-comparator controlled trial of three months duration. Participants will be randomly assigned to either 50,000 IU of vitamin D_3 (n=31) or 5,000 IUs of vitamin D_3 (n=31). **Treatment Dose and Schedule:** The supplements are administered once a week for three months. The dose of vitamin D_3 (cholecalciferol) (50,000 IUs) has been safely used (23, 24, 25). The weekly dosing is being used to increase compliance to therapy (i.e., not having to remember to take it daily) and has been successful in treating other disorders (26). To further increase compliance, participants will receive a weekly automated phone call reminder to take their supplement. Vitamin D_3 has been selected as the treatment since it is the natural form of vitamin D, the more widely used supplement, and now recommended for clinical practice (27). The Institute of Medicine recommends 600 IUs of Vitamin D per day for individuals up to age 70 (28). Thus, the 5,000 IUs dose will approximately follow that recommendation (600 IUs x 7 days= 4200 IUs) and be given once per week. The use of a dose with the minimum recommended amount for comparison is consistent with other studies examining the benefit of vitamin D supplementation on health outcomes (7, 29). Bio Tech Pharmacal, Inc. will prepare the vitamin D_3 supplements and follows Good Manufacturing Practices.

The trial is appropriately registered on clinicaltrials.gov under an Investigational New Drug (IND) number (IND 126491). **Treatment Randomization:** A permuted-block randomization list was developed by an independent statistician and retained by a research pharmacist at the study site. These two staff members were independent from those involved with the conduct of the study. The pharmacist uses the list to assign subjects to treatments. **Blinding.** The study supplements are administered by the pharmacist in a blinded fashion during the study so that the patient and clinical site personnel are not aware of the patient's assigned treatment. **Treatment side effects and unblinding:** All vitamin D levels and calcium levels are reviewed by the study medical monitor (Dr. Mary-Ann Emanuele) at baseline and at three months (study completion). Dr. Emanuele is notified if vitamin D levels are greater than 100 ng/ml or if they experience hypercalcemia. In that case, patients are requested to return for repeat labs within one month of stopping therapy for monitoring purposes.

Sample Enrollment Criteria

A. Enrollment Criteria. Inclusion: 1) Women and men aged 18 to 75 years, 2) Having type 2 diabetes, 3) Having a subjective complaint of a cognitive dysfunction or scoring at least one standard deviation below normal on a cognitive functioning screening test (see Procedures and Measures), 4) Vitamin D level as measured by 25-hydroxyvitamin D (25-

OH D) < 32 ng/mL (7), 5) Under the care of a healthcare provider, 6) Systolic blood pressure ≤160 and diastolic blood pressure ≤100. **Exclusion:** 1) Persons with malabsorption problems (e.g., crohn's disease) since this impacts vitamin D absorption (30), 2) Hypercalcemia since vitamin D may increase serum calcium (31, 32), 3) Use of vitamin D supplements in past 2 months and unwillingness to discontinue for one month prior to study, 4) Severe complications of diabetes (amputation, blindness, and dialysis) 5) currently taking high dose steroids, 6) GFR < 60, 7) Creatinine > 1.2, 8) Having significant depressive symptoms (CESD≥ 16), 9) Having a history of bipolar depression, psychotic disorders, loss of consciousness greater than 5 minutes, or a current alcohol or substance use disorder, 10) Other serious medical conditions deemed significant by the PI or medical monitor, 11) Current use of cholinesterase inhibitors, 12) A new prescription for an anxiolytic within the past 12 months or a dose change to an anxiolytic in the past 12 months (or anticipated dose change while in the study), or taking, kava kava, St. John's Wort, or Ginkgo Biloba, 13) Pregnancy, 14) HbA1c >13%, 15) Having a history of kidney stones (unless origin know to be not calcium), 16) Taking more than 1200 mg of calcium per day which is consistent IOM guidelines, 17) Patients with known vascular disease (including stroke, TIA, lacunar infarcts,).

Study Procedures

Procedures. There will be a phone screening, followed by a baseline visit to recruit and verify enrollment criteria. **A phone call interview** will be conducted which entails study description, a screening for inclusion and exclusionary criteria, followed by the Center for Epidemiologic Scale (CES-D) to ensure they are not depressed and screening for cognitive function using the Controlled Oral Word Association Test and Animal Naming Test (see Appendix for phone call screen and instruments). If the patient meets the inclusion criteria, they will be scheduled for a study visit. If they do not, they will be thanked for their time. If participants do not meet the inclusion criteria because of depressive symptoms, a list of resources will be mailed to them. **At the first baseline visit**, participants will come to the School of Nursing at Loyola (in Maguire). The informed consent document will be reviewed by a qualified member of the research team. Participant's capacity to give written informed consent will be evaluated using the "Evaluation to Sign an Informed Consent for Research" form (attached in Appendix). If a participant is unable to provide informed consent, they will be ineligible to participate. After informed consent is obtained, blood will be drawn (glucose, hemoglobin A1c, vitamin D, calcium, and inflammatory markers). Calcium will be measured in order to follow published guidelines when initiating vitamin D at this dose (50,000 IU) to assess for a therapeutic level (7, 34). Also, physical measures (height, weight, and blood pressure) will be collected. Study subjects will be provided with breakfast or a snack and reminded to take their prescribed medications (if needed). Next, the cognitive functioning tests will be administered by a member of the research team. This will include an evaluation of the premorbid intellect using the word pronunciation test from the Wide Range Achievement Test-IV. A questionnaire booklet will be completed with measurement of self-care behaviors, and the researcher will review the questionnaires for missing data to determine whether items were skipped or not answered due to the participant's choice. The questionnaire booklet will include the Patient Health

Questionnaire 9 tool (9 items). If the patient answers positively to item #9 on this tool which reads, "thoughts that you would be better off dead or hurting yourself in some way," then he or she will be assessed for active suicide ideation using a form that is approved for suicidal ideation in the Sunshine Study 2 Protocol (see attached form). If the patient has active suicidal ideation, Dr. Halaris, psychiatrist will be contacted. If the patient has active suicidal ideation and is deemed to be in need of immediate psychiatric care, a member of the research team will escort the patient to the emergency room. In addition, the patient will be given a list of mental health resources and the patient will not be eligible to participate in the study. The baseline visit will be completed with collection of vital signs and a nursing physical assessment administered by a qualified member of the research team. The total amount of time for the baseline visit will be 2-3 hours. Once enrollment criteria have been met, **the second baseline visit** with a qualified member of the research team will be scheduled to dispense the Vitamin D supplement to the participant. At this visit, the six cognitive functioning tests will be administered again in order to wash-out any practice effects. The weekly medication administration schedule and all subsequent contacts (phone and scheduled visits) will be reviewed. Participants will be informed that, at three months, they will return for physical measurements and evaluation of cognitive functioning and self-care behavior. They will be told that in six weeks a qualified member of the research team will conduct a formal phone call follow-up, where they will be asked about medication compliance and side effects and screening for cognitive function using the Controlled Oral Word Association Test and Animal Naming Test. Upon completion of these verbal and written instructions and a negative pregnancy test (if necessary), the patient will be provided with the randomized vitamin D_3 medication. Following dispensing directions, a qualified member of the research team will ask the subject if they have any questions. The second visit will take two hours or less. At their **three-month visit**, the exact protocol from baseline visit (labs, questionnaires, and cognitive functioning tests) will be followed. The three month visit will take 3 hours or less. A qualified member of the research team will request the study medication bottle to estimate drug accountability by counting any remaining pills. **To forestall attrition and enhance compliance**, we will capitalize on retention strategies that have proven successful in Dr. Penckofer's current NIH study (RO1NR013906), which include free parking and compensation for participants' time. Participants will be compensated in a stepped manner: ($20 at first baseline visit, $25 at second baseline visit, and $30 for completing the study at the three month visit). After the patients have completed the study, a letter (see attached letter) will be sent to them which includes the results of their HbA1c and Vitamin D levels.

Table 1: Scheduled Activities

	Screening	Week 0	Week 2	Week 8	Week 13
Depression Screen	X				
Demographics	X	X		X	X
Cognitive Tests	X	X	X	X	X
Questionnaires		X			X
Vitals		X			X
General Nursing Physical		X			

Blood Draw		X			X
Adverse Event Log		X	X	X	X
Dose Management Log			X	X	X
Concomitant Medication Log		X	X	X	X

4. Measurements.

A. Labs will be measured for each time point by Quest Laboratories which is accredited by the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA). **Serum vitamin D** will be measured by liquid chromatography/tandem mass spectrometry (LC-MS/MS) which is the standard for the measurement of vitamin D and its components. This method provides a total 25 hydroxyvitamin D (25 OH- D) which includes 25 (OH) D_2 and 25 (OH) D_3. Thus, we will be able to determine the effectiveness of vitamin D_3 supplementation. **Calcium** will be measured using a cardiometabolic profile. The **hemoglobin A1c** will be assessed using the DCA analyzer which is the practice in our diabetes center. Also, inflammatory markers will be collected. Potential confounders for vitamin D include sun exposure and diet and will be measured as follows**: (1) Sun Exposure**: Season of study enrollment will also be recorded and the Cancer Sun Exposure Tool which is 14 items and assesses sun exposure and use of sunscreen (35), **(2) Dietary Intake**: The Block Calcium and Vitamin D Screener will be used. This tool was developed from the NHANES 1999-2001 dietary recall data. It includes 19 food items, 3 supplement questions, and questions to adjust for food fortification practices (36).

B. Self-Management measures include: **(1) Diabetes Self-Care Inventory** (15 items) assesses a patient's perceptions of the degree to which they adhere to treatment recommendations for diabetes self-care (1= never do it to 5= always do it). This tool does not presume that all individuals have the same treatment prescription and thus is able to assess adherence to different treatment regimens (e.g., insulin or not taking insulin) (37, 38). **(2) Diabetes-Related Distress (**PAIDS, 20 items) measures the current burden of diabetes and its treatment. The responsiveness of the tool to detect changes in distress has also been established using data from seven prospective diabetes intervention studies (39).

C. Cognitive Functioning measures include six instruments. **(1) The Controlled Oral Word Association Test (COWAT)** is a measure of verbal fluency that assesses the ability to initiate and maintain effort and requires participants to rapidly produce words beginning with certain letters (40). This verbal fluency task taps the function of the dorsolateral prefrontal cortex, a prime target of the atrophy observed in the brains of decedents with diabetes. **(2)The Animal Naming** test is similar to COWAT, but it assesses semantic fluency rather than phonemic fluency. Verbalizing a large amount of words indicates superior performance. **(3) The Letter Number Sequencing** is a test in which a string of alpha-numeric characters are read aloud to the participant, and he/she has to mentally rearrange them and say back all the numbers in numerical order followed by all the letters in alphabetical order (41). Few errors indicate superior performance.

(4)Stroop Interference Test involves having the participant read color words, name colors, and complete an interference condition (i.e., the words are printed in colored ink that does not correspond to the written word). As quickly as possible, the subject must ignore what the word actually says and, instead, name the color of the ink in which the word is printed (42). High scores indicate superior performance. **(5) Digit Symbol Modalities Test** assesses several skills including motor persistence, sustained attention, response speed, and visuomotor coordination (43). Participants must draw in numbers that match symbols as quickly as possible for 90 seconds. Higher scores indicate superior performance. **(6) Trail Making Test Parts A and B** assesses psychomotor processing speed and cognitive flexibility (44). This test requires the participant to view a series of randomly arranged numbers and letters on a page. Participants must draw a line alternating between numbers and letters in numerical and alphabetical order (e.g., 1-A-2-B-3-C and so on), as quickly as possible. Shorter time-to-completion and few errors indicates superior performance. (7) **Hopkins Verbal Learning Test revised** assesses verbal learning and memory. The test asks participants to recall a series of 12 words after a period of 20 to 25 minutes.

D. Other Factors that contribute to the health of individuals with diabetes include **(1)** Pittsburgh Sleep Quality Index (19 items) measures sleep quality (45), **(2)** the Perceived Stressor Scale (10 items) measures stress (46), **(3)** social functioning will be measured using the Social Adjustment Scale-Self Report (24 items) (47), **(4)** exercise using the Godin Leisure Time Exercise questionnaire (2 items) (48), and **(5)** the Endicott Work Productivity Scale (25 items) (49). **(6)** the Patient Health Questionnaire 9 (PHQ9) (9 items), will be used to assess for depression at the baseline visit only.
See attached appendix for all questionnaires and instruments.

Recruitment Procedures

For recruitment of study participants, we will be using the database of Dr. Penckofer which has over 350 patients who have expressed interest to participate in diabetes research in the past few years. See attached letter that will be sent to potential study participants. In our current work (LU 204197), we have been able to reach out to over 1200 patients thus far. Given our previous work, patient recruitment should not be an issue for this pilot study. Also, an approved flyer through Marketing will be distributed at Loyola University Medical Center outpatient centers, places of business who have provided approval, and professional meetings, and 3) A qualified member of the research team will be present at the endocrinology outpatient clinic to provide information about the study to potential participants.

Informed Consent
Informed consent will be obtained by a qualified member of the research team when the patient comes to the School of Nursing (Maguire) for the first in-person visit.

Safety Monitoring Plan

A monitoring plan has been established to ensure that the data remain confidential and that any harm from the intervention is minimized. The research team (including principal investigators, co-investigators, and qualified members of the research team) will meet once a week to assess the activities of the study, including the review of any adverse events, serious adverse events, or noncompliance with the procedures of the protocol.

Study Monitoring Criteria:

The research team will specifically review (1) number (if any) patients who develop vitamin D levels greater than 100 ng/mL or symptoms of vitamin D toxicity, (2) number (if any) patients who developed hypercalcemia, (3) number of patients (if any) who develop systolic blood pressure readings >160 mmHg or diastolic >100 mmHg, (4) number of patients (if any) who develop an increase in creatinine of 25% or more, and (5) patients with significant worsening cognition.

Individual Stopping Criteria

The research team will review data related to individual stopping criteria, as detailed below. The medical monitor may recommend modifications to individual stopping rules if additional safety concerns arise during their continuing review of the study data.

- If Vitamin D levels exceed 100 ng/mL at any time
- If a participant's CA >10.5 at any point
- If a participant develops a kidney stone
- Significant worsening cognition

Worsening cognition will be treated as an adverse event. Participants will be referred to an appropriate healthcare provider (i.e. Neuropsychologist, Clinical Psychologist, Psychiatrist, or Neurologist) by a member of the research team.

Study Stopping Criteria

The medical monitor may recommend stopping the study for the following reasons:

- The data show a significantly increased risk of serious adverse effects deemed related to the study supplement in one of the treatment groups
- It becomes clear that successful completion of the study is not feasible (e.g. there is an excess of patient dropout, missing data, lack of recruitment, etc)

In addition, termination or modification may be recommended for any other perceived safety concern based on clinical judgment, including but not limited to a higher than anticipated rate for any component of the primary endpoint, protocol failures resulting in adverse events, or unexpected adverse events.

Analysis Plan

Statistical Methods: Power

A meta-analysis based on a sample size of N = 7,688 by Etgen et al. (2012) was used to determine a sample size with suitable power for this trial. In their study, individuals with insufficient vitamin D were nearly three times (95% CI: 1.91 – 3.00) more likely to experience executive dysfunction than individuals who were vitamin D sufficient. Our study is powered to test the null hypothesis that performance on a battery of executive functioning tests is equal between individuals receiving high dose vitamin D therapy and those receiving low dose vitamin D therapy. These executive function scores are assumed to be standard scores (μ=100, SD=15).

With a proposed total sample size of 62 subjects assigned to the 50,000 IU and 5,000 IU dose treatment arms using a 1:1 allocation, the study has power of 81.1% to yield a statistically significant result. This computation assumes a two-sided alpha level of 0.05, that the mean difference between the two groups is less than one standard deviation (mean difference = 11.0) which corresponds to expected means of $\mu = 96$ for the 50,000 IU group and $\mu = 85$ for the 5,000 IU dose group, and that the common within-group standard deviation is one standard deviation (or 15 points). This effect was selected as the smallest effect that would be important to detect, in the sense that any smaller effect would not be of clinical or substantive significance. In order to account for attrition, 80 participants are planned to enroll into the study.

Statistical Analysis Plan

Summary frequencies will be reported by treatment allocation for all nominal baseline characteristics, including sex, race, ethnicity, marital status, season of first dose, and physical activity level. Summary statistics will be similarly reported as mean with standard deviation for normally distributed demographics (i.e., age, body mass index, blood pressures and heart rate, and CES-D score), while median with interquartile range will be reported for other summary measures including PHQ-9 score, WRAT-IV reading sub-score, years of education, and laboratory values (i.e., vitamin D level, HbA1c, glucose, creatinine, and calcium).

Regarding performance on the *executive functioning* assessments, linear mixed-effects models will be used to estimate the mean change in participants' standardized scores as a function of elapsed time since baseline, treatment assignment, and their interaction. In this study, patients will contribute multiple scores to the analysis and random intercepts will be allowed for each patient to account for their within-subject correlation using an unstructured covariance structure. Regarding model fit, linearity and normality will be assessed using residual and QQ plots, respectively, while outliers will be assessed using box plots. A similar approach will be used to assess performance on assessments of *language and memory* functioning.

Regarding change in *quality of life* and *functioning* self-report measures (i.e., the SAS-SR; SCI-R; PAID; EWPS; PSQI; MOS; and PSS), each participant's baseline score will be subtracted from his/her week 13 score. Subsequently, an independent samples *t*-

test will be used to compare this change score between participants assigned to the high dose versus those assigned to the low dose. In these comparisons, the distribution of survey scores will be assessed for normality using QQ plots and for outliers using box plots. When survey scores are not normally distributed, an exact version of the Wilcoxon rank-sum test may be used to confirm parametric conclusions.

Finally, summary frequencies will be reported for all reported adverse events during the trial by treatment allocation. This includes the number of affected individuals at risk for the adverse event as well as the number of times the adverse event was reported. All analyses will be completed using SAS version 9.4 (Cary, NC).

Literature Cited

1. Lee JH, Choi Y, Jun C, Hong YS, Cho HB, Kim JE, Lyoo, IK. Neurocognitive changes and their neural correlates in patients with type 2 diabetes. Endocrinology and Metabolism 2014; 29:112-122.
2. Smith MA, Else JE, Paul L, Foster JK, Walker M, Wesnes KA, Riby LM. Functional living in older adults with type 2 diabetes: Executive functioning, dual task performance, and the impact of postural stability and motor control. Journal of Aging and Health 2014; 26: 841-859.
3. Littlejohns TJ, Henley WE, Lang IA, Annweiler C, Beauchet O, Chaves PHM, Fried L, Kestenbaum BR, Kuller LH, Langa KM, Lopez OL, Kos K, Soni M, Llewellyn D. Vitamin D and the risk of dementia and Alzheimer disease. Neurology 2014; 83:1-9.
4. McCann JC & Ames BN Is there convincing biological or behavioral evidence linking vitamin D deficiency to brain dysfunction? FASEB Journal 2008; 22: 982- 1001.
5. Schlog M, Holick MF. Vitamin D and neurocognitive function. Clinical Interventions in Aging 2014; 9: 559-568.
6. Holick, MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clinic Proceedings 2006; 81: 353-373.
7. Holick, MF. Vitamin D deficiency. The New England Journal of Medicine 2007; 357:266-281.
8. Tuligenga RH, Dugravot S, Tabak AG, Elbaz A, Brunner EJ, Kivimaki M, Singh-Manoux A. Midlife type 2 diabetes and poor glycemic control as risk factors for cognitive decline in early old age: A post hoc analysis of the Whitehall II study cohort study. Lancet Diabetes Endocrinol 2014; 2(3): 228-235.
9. Wennberg AM, Gottesman RF, Kaufmann CN, Albert MS, Chen-Edinboro LP, Rebok GW, Kasper JD, Spira AP. Diabetes and cognitive outcomes in a nationally representative sample: the National Health and Aging Trends study. Int Psychogeriatr 2014; 26(10): 1729-1735.
10. Munshi MN, Hayes M, Iwata I, Lee Y, Weinger K. Which aspects of executive dysfunction influence ability to manage diabetes in older adults? Diabet Med 2012; 29(9): 1171-1177.

11. Grober E, Hall CB, Hahn SR, Lipton RB. Memory impairment and executive dysfunction are associated with inadequately controlled diabetes in older adults. J Prim Care Community Health 2011; 2(4): 229-233.
12. Abdel Rahman TT, Mohammed MM, Saad Aldeen AA. Executive function in elderly diabetic patients. Geriatric Gerontol Int 2014; April 21 E-Pub ahead.
13. Winkler A, Dlugaj M, Weimar C, Jockel K-H, Erbel R, Dragano N, Moebus S. Association of diabetes mellitus and mild cognitive impairment in middle-aged men and women. Journal of Alzheimer's Disease 2014; July 7 E-pub.
14. Geijselaers SL, Sep SJ, Stehouwer CD, Biessels GJ. Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review. Lancet Diabetes Endocrinol. 2014; Aug 22. Epub.
15. Annweiler C, Montero-Odasso MM, Llewellyn DJ, Richhard-Devantoy S-R, Duque G, Beauchet O. Meta-Analysis of memory and executive dysfunctions in relation to vitamin D. Journal of Alzheimer's Disease 2013; 37: 147-171.
16. Penckofer S, Kouba J, Wallis D, Emanuele M. Vitamin D and diabetes: Let the sunshine in. Diabetes Educator 2008; 34: 939-954.
17. Gulseth H, Wium C, Birkelad KI. Vitamin D and insulin action and secretion-An overview of current understanding and future perspectives. European Endocrinology 2010; 6(2): 13-18.
18. Davidson MB, Duran P, Lee ML, Friedman TC. High-dose vitamin D supplementation in people with prediabetes and hypovitaminosis D. Diabetes Care 2010; 35: 1-7.
19. Penckofer S, Byrn M, Emanuele MA, Mumby P, Quinn L, Wallis D, Harrison P. Can the sunshine vitamin improve depression, diabetes symptoms, and quality of life in women with diabetes? Annals of Behavioral Medicine 2012; 43: S.270
20. Penckofer S, Doyle T, Mumby P, Byrn M, Emanuele M, Wallis D. Vitamin D supplementation improves depression and cardiovascular risk factors. Diabetes 2013; Suppl. 1: A-201.
21. Alves MR, Yamatmoto T, Arias-Carrion O, Rocha NB, Nardi AE, Machado S, Silva AC. Executive dysfunction impairments in patients with depression. CNS Neuro Disord Drug Targets 2014; 13(6): 1026-1040.
22. Zahodne LB, Nowinski CJ, Gershon RC, Manly JJ. Depressive symptoms are more strongly related to executive functioning and episodic memory among African American compared with Non-Hispanic White older adults. Arch Clin Neuropsychol 2014; 29(7): 663-669.
23. Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. Journal of Internal Medicine 2008; 264: 599-609.
24. Burton JM, Kimball S, Vieth R, Bar-Or A, Dosch H-M, Cheung R, Gagne D, D' Souza C, Ursell M, O'Connor P. A phase I/II dose-escalation trial of vitamin D3 and calcium in multiple sclerosis. Neurology 2010; 74: 1852-1859.
25. Nazarian S, St. Peter JV, Boston RC, Jones SA, Mariash CN. Vitamin D_3 supplementation improves insulin sensitivity in subjects with impaired fasting glucose. Translational Research 2011; 158: 276-281.

26. Recker R, Gallagher R, MacCosbe P. Effect of dosing frequency on biphosphonate medication adherence in a large longitudinal cohort of women. Mayo Clin Proc 2005; 80: 856-861.
27. Holck MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heany RP, Murad MH, Weaver CM. Evaluation, treatment, and prevention of Vitamin D deficiency: an Endocrine society clinical practice guideline. J Clin Endocrinol Meta 2011; 96: 1911-1930.
28. Institute of Medicine of the National Academies. Dietary reference intakes for calcium and Vitamin D. National Academy of Sciences, 2011.
29. Mitri J, Dawson-Hughes B, Hu F, Pittas AG. Effects of vitamin D and calcium supplementation on pancreatic beta cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and vitamin D for Diabetes Melllitud (CaDDM) randomized controlled trial. Am J Clin Nutr 2011; 1-9.
30. Koutkia, P., Lu, Z., Chen, T.C., Holick, M.F. Treatment of vitamin D deficiency due to Crohn's disease with tanning bed ultraviolet light B radiation. *Gastroenterology* 2001; 121: 1485-1488.
31. National Institutes of Health. Dietary Supplement Fact Sheet: Vitamin D. http://dietary-supplements.info.nih.gov/factsheets/vitamind.asp (Accessed 10/27/2014)
32. Lips, P. Which circulating level of 25-hydroxyvitamin D is appropriate? *Journal of Steroid Biochemistry & Molecular Biology* 2004; 89-90: 611-614.
33. Etgen T, Sander D, Bickel H, Sander K, Forstl H. Vitamin D deficiency, cognitive impairment and dementia: A systematic review and meta-analysis. Dement Geriatr Disord 2012; 33(5): 297-305.
34. Wallis, D., Penckofer, S., Sizemore, G. Contemporary Issues in Cardiovascular Medicine: The Sunshine Deficit and Cardiovascular Disease. Circulation 2008; 118: 1476-1485.
35. Glanz K, Yaroch AL, Dancel M, Saraiya M, Crane LA, Buller DB, Manne S, O'Riordan DL, Heckman CJ, Hay J, Robinson JK. Measures of sun exposure and sun protection practices for behavioral and epidemiologic research. Arch Dematology 2008; 144(2): 217-222.
36. Cummings SR, Block G, McHenry K, Baron RB. Evaluation of two food frequency methods of measuring dietary calcium intake. Am J Epidemiol 1987; 126:796-802.
37. Greco P, LaGreca A, Ireland S, Wick P, Freeman C, Agramonte R, Gutt M, Skyler J. Assessing adherence in IDDM: A comparison of two methods: Diabetes 1990; 40 (Suppl. 1): A 165.
38. LaGreca AM. Brief Manual for the Self-Care Inventory. 1992. Miami, FL: LaGreca.
39. Welch, G., Weinger, B, Anderson B, Polonsky WH. Responsiveness of the problem areas in diabetes (PAID) questionnaire. Diabetic Medicine 2003; 20: 69-72.

40. Ruff RM, Light RH, Parker SB, Levin HS. Benton controlled oral word association test: Reliability and updated norms. *Archives of Clinical Neuropsychology 1996*; *11*: 329-338.
41. Wechsler, D. *WAIS-IV: Wechsler Adult Intelligence Scale*. 2008; Pearson.
42. Stroop, JR. Studies of interference in serial verbal reactions. *Journal of Experimental Psychology 1935*; *18*: 643.
43. Smith, A. *Symbol digit modalities test: Manual*. 2002; Western Psychological Corporation.
44. Reitan, RM. Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills 1958*; *8*: 271-276.
45. Buysse DJ, Reynolds CF, Monk TH, Berrman SR, Kupfer DJ. The Pittsburg Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research 1998; 28*: 193-213.
46. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *Journal of Health and Social Behavior 1983*; 24(4): 385-396.
47. Gameroff, M.J., Wickramaratne, P., & Weissman, M.M. (2012). Testing the short and screener versions of the social adjstument scale-self report (SAS-SR). *International Journal of Methods in Psychiatric Research, 21*(1), 52-65.
48. Godin, G., Shephard, R. J. (1997). Godin leisure-time exercise questionnaire. *Medicine and Science in Sports and Exercise*. 29 June Supplement: S36-S38.
49. Endicott, J., & Nee, J. (1997). Endicott work productivity scale (EWPS): A new measure to assess treatment effects. *Psychopharmacology Bulletin*, *33*(1), 13-16.