

Protocol: AAAF1797

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Title: Randomized controlled trial of Vitamin D Repletion Regimens in Primary Hyperparathyroidism

Study Purpose and Rationale:

Vitamin D deficiency is very common in the setting of PHPT, and leads to higher PTH levels. In this study, we will investigate the impact of two different vitamin D repletion regimens over a six month period in patients with PHPT and concurrent vitamin D deficiency. We hypothesize that vitamin D repletion ameliorates the extent of hyperparathyroidism and improves biochemical, microarchitectural and biomechanical features of the disease. In addition, we will show that vitamin D can be repleted safely in patients with PHPT. This would be of great importance to the many physicians treating patients with PHPT today, who are being advised to replete vitamin D in these patients without any clear guidelines as to how best to do so.

Study Design:

40 patients with PHPT and vitamin D deficiency (25OHD less than 30 ng/ml) will be enrolled and randomized 4:1 to two different vitamin D repletion regimens. Randomization to treatment will use randomly permuted blocks. Our first group will receive 2 capsules of 10,000 IU of vitamin D once per week for the first month and then 1 capsule of 10,000 IU of vitamin D once per week for the remaining five months which should replete vitamin D deficiency and decrease PTH (our primary end-point). Control subjects (Group 2) will take 2 capsules of the placebo once per week for the first month and then 1 capsule of the placebo once per week for the remaining five months. All subjects will receive 400 IU of vitamin D each day, either in the form of a multivitamin or by itself, for the entire study. Our protocol provides 400 IU of vitamin D per day for control subjects because we felt that ethically it would not be appropriate to withhold all vitamin D from this group. A 400 IU dose is expected to raise serum 25-OHD levels minimally (2-3 ng/ml) thus allowing this cohort to serve as a valid control group ¹.

Study drug will be dispensed at the first visit as appropriate to randomization. Participants will be instructed on and receive a printed medication administration schedule. They will be advised to begin taking their study drug immediately, and up to 500 mg of supplemental calcium but no additional vitamin D. They will be instructed about events that could be related to hypercalcemia or hypercalciuria: nephrolithiasis, nausea, vomiting, polyuria/polydipsia, or fractures.

The study will have a 6 month design, which will allow us to capture our treatment groups before and during the process of becoming vitamin D replete. Many PHPT patients are monitored without surgery for years and thus determining the safety and effect of maintaining adequate 25-OHD levels is imperative.

No vitamin D toxicity data exist in patients with PHPT. Available data in normal subjects are of limited applicability to patients with PHPT who are hypercalcemic and often hypercalciuric at the outset. However, in normal subjects hypercalcemia does not occur unless serum 25-OHD levels are above 150-200 ng/ml. The Food and Nutrition Board has set a safe tolerable upper intake level of 2000 IU daily for vitamin D3 and 2400 IU as the no-observed adverse-effect level. More recent clinical trial data suggest that these assessments are extremely conservative ². It should be noted that none of the patients

treated by Grey et al. achieved a 25-OHD level above 50 ng/ml, and their mean increment in 25-OHD was 19 (range 6-37 ng/ml). However, because PHPT patients may be more susceptible to adverse effects due to their baseline elevations in serum and urinary calcium, the careful monitoring we propose is essential to allow conclusions about safety of repleting vitamin D in PHPT. In addition, because of this concern, we will exclude any patient with: serum calcium greater than 11.5 mg/dL; urine calcium greater than 350 mg/dL per day; active nephrolithiasis or nephrocalcinosis. We will also compare the percentage of participants who achieve a 25-OHD level above 30 ng/ml in each group, and assess the changes in serum and urinary calcium, 25-OHD and 1,25-OH₂D among groups. We will describe the time course of the normalization of 25-OHD levels in the treatment group and evaluate whether the level of vitamin D or acuity of the change in vitamin D is predictive of adverse events. We plan to analyze the data on an intent-to-treat basis, but will also do a secondary per protocol analysis based upon final vitamin D level in order to estimate achievable PTH reduction in regimen compliant subjects. Finally, we will assess patients for the development of safety outcomes. Participants whose serum calcium concentration rise above 12 mg/dL or develop nephrolithiasis (evaluation of clinical complaint) will be withdrawn. Although we will also monitor and compare the number of participants in each group whose urinary calcium level exceeds 400 mg/day, these individuals will not be withdrawn as explained in the Data and Safety Monitoring section. The frequency of patients with these outcomes at each time point will be compared among groups. We expect that the treatment regimen will be effective in achieving a vitamin D level above 30 ng/ml, while the 400 IU control group will not reach this threshold. The issues assessed here will therefore be of great value in formulating recommendations for vitamin D treatment, a key research goal of the new Consensus Guidelines, and an imperative for clinicians treating PHPT patients.

Describe how participants will be recruited:

Patients with primary hyperparathyroidism will be recruited by physician referral from the population of patients seen in the Metabolic Bone Diseases Unit, Endocrine Clinic, and the Surgical Endocrine Unit. During a medical visit, eligible patients will receive information about the study and study procedures by their physician. Those patients interested in the study will give their permission to have their contact information sent to the study coordinator and PI for follow-up. Patients who do not want to hear more information about the study will not be contacted. Those patients who agree to hear more information about the study will be contacted by the PI or the study coordinator. The patient will learn more about the study, study procedures, and the consent form. Those who agree to participate will have the consent form mailed to them for further review. During their first visit, the study coordinator, or the physician, will go over the consent form and answer any other study related questions, the participant will then sign the consent form. The availability of patients from both the medical and surgical services at Columbia University Medical Center (CUMC) over the funding period should provide ample opportunity for us to enroll patients.

Statistical Procedures:

The primary statistical analysis of the 6-month endpoint will be an intent-to-treat (ITT), "as prescribed", ANCOVA assessment of between group differences in log-transformed serum PTH level adjusted for baseline serum PTH and the covariates listed below. The primary ITT analysis will be repeated with actual cumulative vitamin D intake entered as a continuous time-dependent covariate to estimate the time course of the "as treated" decrease in PTH level. Analysis of the longitudinal growth curve of each

measure will use linear mixed models for repeated measures to assess the fixed effects of vitamin-D repletion regimen, time, regimen time interaction, random effects for intercept and standard covariates; and a covariance structure fit prior to the hypothesis test. Average time to achieve a 25-OHD level of 30 for the two vitamin-D repletion regimens will be estimated with a Cox proportional hazards model. Power and sample size calculations assume PTH is analyzed in log units, unequal sample sizes in the two groups, unequal variances in the two groups, a type I error rate of 0.05, 80% power and a two-tailed T-Test of the post-treatment PTH levels. A reduction in the treated group from 149 ± 64 ng/ml to 85 ± 48 pg/ml is larger than our original estimated effect size but consistent with the data available from our cross-sectional study for patients with 25OHD 30 ng/ml, respectively. Given the above assumptions and a desired 4:1 treatment allocation ratio, a sample size of 40 distributed 32 vs 8 meets our power goal (calculated with harmonic mean sample size of 13 per group). The analysis of safety event rates will include Fisher's Exact comparisons of between-group differences in the number of patients with hypercalcemia and/or hypercalciuria; and a Cox proportional hazards assessment of time to first AE adjusted for standard timeindependent covariates and time-dependent cumulative vitamin D dosage will be used to estimate the contribution of vitamin D to the development of the safety events. Assessments of safety events will be conducted to relate the onset of safety events to baseline vitamin-D levels, to the ramp of vitamin-D level increase and peak available vitamin-D level at time of event (to the extent known). Standard covariates for all analyses include season, weight, serum calcium and age. All power and sample size calculations based on SAS Power and Sample Size 3.1 (SAS Institute, Cary, NC).

References:

1. Hatcheck JN, Shao A, Vieth R, Heaney R 2007 Risk assessment for vitamin D. *Am J Clin Nutr* 85:6-18
2. Ambrogini E, Cetani F, Cianferotti L, Vignali E, Banti C, Viccica G, Oppo A, Miccoli P, Berti P, Bilezikian JP, Pinchera A, Marcocci C 2007 Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective, randomized clinical trial. *J Clin Endocrinol Metab* 92:3114-3121