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IRB Proposal

Study rationale and design

The leading cause of death in patients with chronic kidney disease (CKD) is cardiovascular disease. The rate of cardiovascular events in patients with CKD appears to be out of proportion to traditional risk factors, such as hypertension, diabetes, coronary artery disease. A new field of research about low vitamin D levels in chronic kidney disease suggests an association between low vitamin D levels and increased cardiovascular mortality. Risk factors for low vitamin D levels include older age, obesity, diabetes, African descent, female gender, and CKD. The mechanism behind low vitamin D levels (25-OH D) in CKD may be because of loss of vitamin D binding protein in the urine and decreased photocoversion of vitamin D sterol in the dermis of patients with CKD, whereas the low levels of 1-25 OH D (activated vitamin D) is likely due to decreased 1-a hydroxylation in the kidney.

The mechanism behind vitamin D deficiency and cardiovascular disease is thought to be due to the extra-skeletal effects of vitamin D on vascular tissue[i]. There is a paucity of randomized control trials (RCTs) on Vitamin D and the primary outcome of cardiovascular events. Endpoints studied thus far are blood pressure, albuinuria, lipids, and left ventricular hypertrophy, all of which are elevated in low vitamin D states[ii],[iii].

Studies on patients with lower stages of CKD (stage I – II) have shown that vitamin D levels may predict progression to end stage renal disease (ESRD) and death[iv]. Vitamin D therapy has shown to improve survival in patients initiating hemodialysis (HD). This association appears to be most significant at vitamin D levels < 10ng/ml[v]. A prospective study in patients without CKD showed increase in cardiovascular disease in patients with vitamin D levels < 20ng/ml. Observational studies on HD patients showed improved survival with calcitriol supplementation. A metaanalysis in 2007 on 76 RCTs about vitamin D supplementation in CKD showed that insufficient randomized evidence was present to make formal conclusions on effect of vitamin D on mortality, cardiovascular outcomes, and fractures[vi].

Furthermore, vitamin D may also have other beneficial effects on patients with CKD, namely better immune system. Hubel et al[vii] noted an increase in phagocytic function in patients on HD who received activated vitamin D supplementation.

Given the high prevalence of vitamin D insufficiency in the CKD population, a study showing vitamin D supplementation leading to decreased cardiovascular disease will change the landscape of risk factor reduction in CKD patients.

Study design and statistical procedures

Randomized control, double-blinded study investigating the effect of vitamin D supplementation on cardiovascular disease in patients with estimated glomerular filtration rates (eGFR) between 15 and 90, which corresponds to CKD stages II - IV.

The event rate was estimated using three RCTs in the CKD population, the SHARP trial, Darbepoetin in CKD and DMII trial, and Rosuvastatin and patients undergoing HD Trial. The estimated rate of cardiovascular events, annually, was around 12%.

Given an estimated event rate of 25% (P1) in the control group, over two years, and 20% (P2) in the intervention group, over two years, the following number of subjects need to be recruited for the study to have 80% power to detect a 5% difference between the groups, $p < 0.05$:

8 (P1Q1 + P2Q2)/Effect2 + P1Q1/Effect + 2 where Q is (1 – P) and Effect =P1 – P2

= 1152 patients in each arm of the study

An effect size of 5% was chosen because it is clinically relevant given the low cost and good side effect profile of treatment. There are no RCTs that have established event rate reduction in CVD with Vitamin D supplementation.

Study procedures

Patients with eGFR between 15 and 90 and serum 25-OH D levels >10 will be randomized to receive vitamin D supplementation with cholecalciferol (1000IU daily) versus placebo with median follow-up of two years. Serum calcium, phosphorus and PTH levels will be checked every three months to ensure safety. Rescue vitamin D will be given to patients whose levels drop <10ng/ml. Once these levels return to >10ng/ml, rescue treatment will be stopped and patients will follow protocol according to their study arm. Patients will be required to see healthcare professionals every three months to control traditional risk factors for cardiovascular disease, such as hypertension, diabetes, cholesterol.

Interim analsysis will be performed to determine safety of study. If clear survival advantage is shown before study is complete, study will be terminated according to IRB recommendations.

Study drugs or devices

Vitamin D supplementation increases whole body vitamin D stores. Activated vitamin D binds to vitamin D receptors throughout the body, including receptors on endothelial cells. Given the recent change in KDOQI guidelines regarding screening for vitamin D deficiency/insufficiency in patients with CKD stage III – V, vitamin D supplementation in the United States has increased dramatically and has proven to have a low side effect profile.

Study subjects

Inclusion criteria: Age > 18 years, eGFR between 15 – 60 as estimated by MDRD, Vitamin D level >10ng/ml, ability to consent

Exclusion criteria: Vitamin D level >30ng/ml, PTH level above target range for CKD stage as specified in KDOQI guidelines, use of anti-seizure medications, known osteoporosis

Primary measured outcome is hospitalization for cardiovascular disease, include fatal or non-fatal MI, stroke, TIA, need for revascularization.

Secondary outcomes are fracture, hospitalization for infection, progression to ESRD.

Confidentiality of study data

All patient data will be stored on 128-bit encrypted device. Only researchers on the IRB protocol will be involved in patient recruitment. All patient data will only be used for purposes of this study.

Risks

Toxicity from vitamin D supplementation is rare and occurs secondary to hypercalcemia, hyperphosphatemia, and oversuppression of PTH. The Institute of Medicine has set the upper limit of tolerability at 4000IU/day. Serum levels of vitamin D > 60ng/ml are toxic and increase risk of pancreatic cancer, vascular calcification and death. [viii]

Patients in the control group who do not receive vitamin D supplementation may be at increased risk for metabolic bone disease and cardiovascular disease. Therefore, patients with PTH greater than the target range specified by KDOQI guidelines will not be eligible to participate.

Benefits

Given the association between cardiovascular disease and low vitamin D levels, the patients enrolled in the study arm may have improved cardiovascular outcomes as a result of vitamin D supplementation.

Alternatives

None applicable

[i] Zitittermann A, Schleithoff SS, Koerfer R. Putting cardiovascular disease and vitamin D insufficiency into perspective. Br J Nutr. 2005; 94:483-492

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[iii] Lind L, Hanni A, Lithell H, Hvarfner A, Sorensen OH, Ljunghall S. Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men. Am J Hypertens. 1995; 8:894-901

[iv] Ravani et. Al. Vitamin D levels and patient outcomes in chronic kidney disease. Kidney Int. 2009 Jan;75(1):88-95. Epub 2008 Oct 8.

[v] Wolf M, Shah A, Gutierrez O *et al*. Vitamin D levels and early mortality among incident hemodialysis patients. Kidney Int 2007; 72: 1004–

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[viii] Clifford J. Rosen, M.D. Vitamin D Insufficiency. N Engl J Med 2011; 364:248-254