CRC IRB Proposal
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The effect of supplementation with vitamin D on recurrent ischemic events and sudden cardiac death in patients with acute coronary syndrome

Study Purpose and Rationale

With advancements in science and technology leading to a decrease in sun exposure and current dietary habits, vitamin D deficiency and insufficiency are extremely prevalent in society today. Studies estimate that up to 40% of community dwelling US adults are currently vitamin D deficient (defined by some as a serum concentration of < 20 ng/mL), and a greater portion being vitamin D insufficient (defined by some as a serum concentration of 21-29 ng/mL).[1] The primary source of vitamin D in the human body occurs through exposure of UV radiation to skin, which causes a conversion of 7-dehydrocholesterol to vitamin D3 at levels that far exceed that found in dietary sources.[2] Supplementation is a secondary source of vitamin D, common women and elderly patients as prevention or treatment for osteoporosis.

There has been thought that vitamin D deficiency may lead to increased risk for several chronic diseases, including cancer, bone disease, autoimmune disease, hypertension, and cardiovascular disease.[3] Many tissues in the human body express a nuclear vitamin D receptor linked to a signal transduction pathway, as well as possess the ability to convert inactive vitamin D to its active form. Thoughts that vitamin D may be able to regulate gene expression through its action on these receptors has offered a plausible explanation for the hypothesized benefits of vitamin D.[4]

One such area of expression is vascular smooth muscle cells. Through these cells, vitamin D regulates the expression of many proteins relevant to the arterial wall, including endothelial growth factor, myosin, elastin, type I collagen, and matrix metalloproteinases.[5] Alteration in the regulation of such elements may lead to significant changes in the vascular structure. Past studies have shown an inverse relationship with vitamin D levels and development of atherosclerosis,[6,7] as well as coronary artery calcification, a marker for atherosclerosis.[8,9]

Increased propensity to develop atherosclerosis and other alterations in vasculature in vitamin D deficient and insufficient patients may lead to an increased risk of coronary heart disease. Indeed, this was demonstrated in multiple trials. In the Health Professionals Follow-up Study (HPFS), a prospective cohort of more than 50,000 male patients aged 40 to 75; patient data was collected for several years through surveys, telephone calls, chart reviews, and laboratory tests. A recent study analyzed vitamin D levels in stored blood of over 18,000 participants in the HPFS and tracked outcomes regarding cardiovascular disease. Analysis revealed an increased risk of non-fatal MI or fatal CHD for subjects in the vitamin D deficient group as compared to those in the vitamin D sufficient group.[10] Another study that analyzed over 10,000 patients in a cardiology practice showed an increased risk for several cardiovascular diseases including hypertension, CAD, cardiomyopathy, and diabetes, as well as mortality

in patients who were vitamin D deficient. Additionally, supplementation with vitamin D was shown to improve survival in this cohort of patients.[11]

Whether through effects on the progression of atherosclerosis, antioxidant effects, or other unknown mechanisms, there is evidence to suggest that vitamin D may have a protective effect on coronary heart disease. To my knowledge, there have not yet been any randomized controlled trials assessing the effect of supplementation with vitamin D on outcomes of patients with known cardiovascular disease despite multiple studies suggestive of benefit. I would like to study the effect of vitamin D supplementation on those patients with known coronary heart disease to determine if there is any effect on outcomes in these patients.

Study Design and Statistical Analysis

This study will be a blinded, randomized controlled trial to study the effects of vitamin D supplementation on outcomes in patients with known CAD.

Patients to be considered for the trial will be all patients who present to New York Presbyterian Hospital – Columbia University Medical Center with a diagnosis of acute coronary syndrome (ACS; STEMI, NSTEMI, or unstable angina) within the predefined study period. Patients will be assessed for presenting diagnosis, baseline medical status, disease severity using APACHE II score, and comorbidity measured using the Charlson Comorbidity Index. Baseline lab values will be obtained and blood samples will be stored for future analysis. Patients will be randomized to receive either vitamin D supplementation with the standard dose of 800 IU of cholecalciferol (inactive, unhydroxylated vitamin D3) daily or placebo through the duration of the study period. Patients will otherwise be treated in an identical manner and with the standard medication regimen. Enrollment in the study will occur for 3 years, and follow up will occur for 2 years following the last date of enrollment. Outcomes of this study will be recurrence of ischemic cardiac events, via a composite endpoint of fatal or non-fatal myocardial infarction or sudden cardiac death. Patients will be assessed at the end of the study period through chart review and by telephone interview. Stored blood samples may later be analyzed for serum vitamin D level to assess patient baseline vitamin D status for further study.

Statistical analysis will be performed using chi-squared testing for the composite outcome in subjects in the intervention group compared to subjects in the placebo group. Data will be adjusted for diagnosis on initial presentation, severity of illness, and comorbidities. NYP hospital data reported 387 cases of acute myocardial infarction in the 2005-2006 year. Including a proportionate number of cases of UA, there were approximately 550 cases of ACS during that 1 year period. Assuming 500 annual cases of ACS at NYP during the study period, and approximately 80% participation in the study, the total study population would be approximately 1200 at the end of the 3 year enrollment period. Enrollment of 1200 would allow 600 subjects in the intervention arm, and 600 subjects in the placebo arm. Assuming an incidence of 20% occurrence of the composite endpoint in the control group during the follow-up period,[12] a 6% difference in incidence would be required in the intervention group for the study to be sufficiently powered.

Study Procedures

Not applicable.

Study Drugs

Vitamin D in the form of cholecalciferol is currently approved for treatment and prevention of osteoporosis, vitamin D deficiency, and supplementation.

For rationale of use, see background information.

The drug will be administered via the oral route at a dose of 800 international units a day, one of many common dosing regimens.

Excess vitamin D intake may increase the risk of falls or fractures. Other potential adverse effects include increased risk of urinary tract infections, decreased appetite, weight loss, an elevated international normalized ratio, hypercalcemia (increased calcium in the blood), hypercalciuria (increased calcium in the urine), hypervitaminosis D (high blood levels of vitamin D), elevated creatinine levels, gastrointestinal complaints, and increased cancer risk. The Institute of Medicine (IOM) released a report on November 30, 2010, recommending vitamin D upper intake levels 4,000 IU for those over nine years old, and so side effects at this dose would be very uncommon.

Medical Device

Not applicable.

Study Questionnaires

Not Applicable.

Study Subjects

Inclusion criteria: All patients who present to NYP-CUMC during the predefined study period with a diagnosis of ACS who are able to give consent to participate in the study.

Exclusion criteria: Terminal status within the first 48 hours, medical treatment with vitamin D therapy, self-reported current vitamin D supplementation, inability to consent or refusal to participate in the study.

Recruitment of Subjects

There will be no active recruitment of subjects, as participation will be limited to those who present to NYP-CUMC with a diagnosis of ACS.

Confidentiality of Study Data

All data will be accessible only to investigators.

Potential Conflict of Interest

There is no conflict of interest to report.

Location of the Study

The study will be conducted at the New York Presbyterian Hospital – Columbia University Medical Center Campus. Investigation will occur within the cardiology department.

Potential Risks

There is the potential for adverse side effects associated with supplementation with vitamin D. However, the level of supplementation is far below that of the maximum approved dose. Studies have shown extremely high levels of supplementation are required for toxicity.[13] Nonetheless, patients will be informed of potential side effects before enrollment. All patients will receive the standard medical treatment for their condition in addition supplementation with vitamin D or placebo.

Potential Benefits

The potential benefits to the patient are a possible reduction in further occurrence or cardiovascular disease or death as demonstrated in previous studies. Additionally, supplementation with vitamin D can potentially improve bone mineral density as previously studied.

Alternative Therapies

Not applicable.

Compensation to Subjects

Subjects will not be compensated for participation.

Cost to Subjects

Subjects will incur no additional costs as the vitamin D or placebo will be provided to the patient.

Minors as Research Subjects

Not applicable.

Radiation and Radioactive Substances

Subjects will not be exposed to radiation or radioactive substances beyond the usual and standard treatment for their condition.

References

1 Chapuy, M. C., Preziosi, P., Maamer, M., Arnaud, S., et al. Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos. Int. 1997, 7, 439–443.

2 Holick, M. F., Chen, T. C., Lu, Z., Sauter, E. Vitamin D and skin physiology: a D-lightful story. J. Bone Miner. Res. 2007, 22, V28–V33.

3 Peterlik, M., Cross, H. S. Vitamin D and calcium deficits predispose for multiple chronic diseases. Eur. J. Clin. Invest. 2005, 35, 290–304.

4 Revelli, A., Massobrio, M., Tesarik, J. Nongenomic effects of 1alpha,25-dihydroxyvitamin D(3). Trends Endocrinol. Metab. TEM 1998, 9, 419–427.

5 Norman PE, Powell JT. Vitamin D, shedding light on the development of disease in peripheral arteries. Arterioscler Thromb Vasc Biol. 2005;25(1):39-46.

6 Lim S, Shin H, et al. Vitamin D inadequacy is associated with significant coronary artery stenosis in a community-based elderly cohort: the Korean Longitudinal Study on Health and Aging. J Clin Endocrinol Metab. 2012 Jan;97(1):169-78. Epub 2011 Oct 19.

7 Shanker J, Maitra A, et al. Role of vitamin D levels and vitamin D receptor polymorphisms in relation to coronary artery disease: the Indian atherosclerosis research study. Coron Artery Dis. 2011 Aug;22(5):324-32.

8 Watson KE, Abrolat ML, et al. Active serum vitamin D levels are inversely correlated with coronary calcification. Circulation. 1997 Sep 16;96(6):1755-60.

9 de Boer IH, Kestenbaum B, et al. 25-hydroxyvitamin D levels inversely associate with risk for developing coronary artery calcification. J Am Soc Nephrol. 2009 Aug;20(8):1805-12. Epub 2009 May 14.

10 Forman JP, et al. Vitamin D intake and risk of incident hypertension: results from three large prospective cohort studies. Hypertension. 2005 Oct;46(4):676-82. Epub 2005 Sep 6.

11 Vacek JL, Vanga SR, Good M, Lai SM, Lakkireddy D, Howard PA. Vitamin D deficiency and supplementation and relation to cardiovascular health. Am J Cardiol. 2012 Feb 1;109(3):359-63. Epub 2011 Nov 8.

12 Jokhadar M, Jacobsen SJ, Reeder GS, Weston SA, Roger VL. Sudden death and recurrent ischemic events after myocardial infarction in the community. Am J Epidemiol. 2004 Jun 1;159(11):1040-6.

13 Glade MJ. A 21st century evaluation of the safety of oral vitamin D. Nutrition. 2012 Apr;28(4):344-56.