Hypovitaminosis D Correction and High-Sensitivity C-Reactive Protein Levels in Hypertensive Adults

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Abstract

Context: Hypovitaminosis D has been implicated as a possible risk factor for the development of cardiovascular disease. High-sensitivity C-reactive protein (hs-CRP) has been one of the most extensively studied biomarkers for cardiovascular inflammation as an indicator of disease and event risk, independent of traditional risk factors. To date, it is unclear if correction of hypovitaminosis D leads to a reduction of hs-CRP in human subjects.

Objectives: To assess laboratory validity of 25-hydroxyvitamin D (25-OH-vitamin D) and hs-CRP measurements and to determine whether hs-CRP levels in adults with well-controlled hypertension and comorbid low vitamin D levels changed after hypovitaminosis D correction to a serum 25-OH-vitamin D level greater than 30 ng/mL.

Design: Prospective study using an unblinded design.

Results: One hundred eight subjects who were vitamin D insufficient or deficient completed this study. The mean 25-OH-vitamin D level was 20.07 ng/mL before treatment and 43.92 ng/mL after treatment. Posttreatment vitamin D levels were in the normal range for 91% of the subjects. No statistically significant changes in hs-CRP level were detected after the vitamin D treatment was administered and a posttreatment vitamin D level above 30 ng/mL was confirmed.

Conclusion: We did not detect a statistically significant difference in hs-CRP after correction of hypovitaminosis D. Twelve weekly oral doses of 50,000 IU of ergocalciferol corrected the hypovitaminosis D in more than 90% of cases.

Introduction

Hypovitaminosis D has been implicated as a possible, under-appreciated risk factor for the development of cardiovascular disease. For example, among the Framingham Offspring cohort with hypertension, a twofold increased risk of cardiovascular events was found in patients deficient in vitamin D.

There are possible mechanisms by which vitamin D reduces vascular damage. Experimental observations indicate that vitamin D suppresses the renin gene as well as having direct vascular effects such as modulating smooth muscle cell proliferation, inflammation, and thrombosis. Vitamin D inhibits cholesterol uptake in macrophages, and a vitamin D-deficient-environment leads to foam cell development in patients with diabetes.

In small clinical trials, vitamin D supplementation has promoted improved blood pressure measurements, left ventricular hypertrophy, and inflammatory cytokine levels. However, to date, it is not known if correction of this deficiency leads to any improved clinical outcome. Short courses (8 to 12 weeks) of vitamin D supplementation in deficient individuals, even at doses of 50,000 international units (IU) weekly, have not been shown to result in vitamin D toxicity. Some investigations suggest that a daily oral vitamin D intake up to 2000 IU (100 μg) is safe in the adult population.

There are barriers to optimal trials of vitamin D supplementation in cardiovascular disease prevention. Randomizing patients with moderate to severe vitamin deficiency to a long-term placebo arm could be considered unethical once hypovitaminosis is identified in an individual. Also, a primary prevention trial of vitamin D supplementation would require a very large sample. Therefore, it seems reasonable to search for surrogates that might identify subgroups most likely to benefit from hypovitaminosis D correction.

The most extensively studied biomarker of inflammation in cardiovascular diseases is C-reactive protein, for which standardized high-sensitivity assays are now widely available. In both primary and secondary prevention trials involving statins, the “greatest clinical event reduction has been noted in patients who achieved low-density lipoprotein cholesterol levels below 70 mg/dL and high sensitivity C-reactive protein (hs-CRP) levels under 2 mg/L (and to a greater degree with hs-CRP levels < 1 mg/L).”

Up to 14% of major cardiovascular events occur in patients who have none of the traditional risk factors. It would be of great benefit to determine whether correction of vitamin D deficiency in selected patients would push elevated hs-CRP levels down to the lowest tertile and thus potentially add another anti-inflammatory weapon against some of the major causes of death in the US.

Methods

Subjects and Data

The study design and methods were approved by the Southern California Permanente Medical Group institutional review board. Informed consent was obtained. This study was a prospective study using an unblinded design. Patients were identified in the Kaiser Permanente (KP) electronic medical record database at the KP Fontana Medical Center in California.
Subjects were advised not to take any calcium or other vitamin D supplements during the study period and to report any illnesses. Inclusion criteria were as follows: 1) age 55 years or older, 2) a diagnosis of hypertension (based on 2 blood pressure measurements of ≥ 140/90 mm Hg), 3) blood pressure controlled with medication and lifestyle therapies (< 140/90 mm Hg), and 4) a serum 25-hydroxyvitamin D (25-OH-vitamin D) level below 30 ng/mL (the Medical Center’s laboratory standard). Subjects were excluded if they had any of the following: 1) a preexisting diagnosis of vitamin D deficiency, 2) uncontrolled or secondary hypertension, 3) any of a number of other cardiovascular conditions, 4) treatment with statin medication, 5) long-term corticosteroid use, 6) cancer, 7) abnormal serum calcium levels or parathyroid disease, or 8) infection (viral, bacterial, or other) within 1 month preceding the collection of blood samples for hs-CRP analysis.

Statistical Analysis

Paired t-tests were used to examine the change of hs-CRP and 25-OH-vitamin D values. The Wilcoxon signed rank sum test was used if a non-normal distribution was observed. Pearson/Spearman correlation coefficient, linear regression, and analysis of covariance assessed the associations between log-transformed measurements of hs-CRP and 25 OH-vitamin D, controlling for baseline demographics and reported dietary vitamin D intake. Significance level was defined as p < 0.05. The software SAS Enterprise Guide was used for all analyses (version 4.3, SAS Institute Inc, Cary, NC).

Results

A total of 327 adult hypertensive subjects were screened for vitamin D deficiency, and 142 (43%) of the subjects had low serum vitamin D levels (< 30 ng/mL). Analysis included 108 patients who completed all aspects of the study. The main reason that subjects failed to complete the study was failure to undergo the required blood tests in a timely manner. The mean age of the study subjects was 64.5 years. This study was composed of 37% white, 19.4% African-American, and 14.8% Hispanic individuals. The remainder declined to state their racial background. Women made up 63% of the participants (Table 1).

There was no statistically significant difference between the first and second measurements of pretreatment vitamin D, or pretreatment and posttreatment hs-CRP. There was, however, a significant difference between the first and second posttreatment measurements of vitamin D (< 0.001). The first posttreatment measurements were, on average, 6.8 ng/mL higher than the second measurement of posttreatment vitamin D. The 2 measurements of pretreatment vitamin D, pretreatment hs-CRP, and posttreatment hs-CRP were statistically similar, with a p-value range from 0.61 to 0.96 (Table 2).

There was no significant difference of median hs-CRP levels between pretreatment and posttreatment values (Table 3). After log transformation, there was no significant decrease between log-transformed pretreatment and posttreatment hs-CRP levels.
The results indicated that 12 weeks of treatment were sufficient to correct vitamin D deficiency. The average vitamin D level increased from 20 ng/mL to 40.5 ng/mL. No significant changes in hs-CRP level were found because of a large variation of hs-CRP values. The posttreatment hs-CRP level may be associated with the initial degree of vitamin D deficiency. This is supported by a trend toward significance (p = 0.056) (Figure 2).

Discussion

Our main finding in this study was that correction of hypovitaminosis D had no statistically significant effect on hs-CRP levels in patients with hypertension and with no other major disease states. We did confirm that a 12-week treatment with ergocalciferol was effective treatment for hypovitaminosis D. However, these data suggest that such gains may be fleeting and that ongoing oral vitamin D supplementation is likely required to maintain normal serum vitamin D levels.

Our study has a number of limitations. First, this was a pilot study with limited power to discern subtle changes in hs-CRP. We estimate that 1441 subjects would be needed to observe a significant change at the 0.05 level with 80% power, assuming that the observed results were similar in a larger study. Second, the patients in the study were predominantly women and the mean age was age 64.5 years, possibly limiting the application of data to other populations. Third, the exclusion criteria were restrictive. Fourth, the study follow-up period of 12 weeks for most subjects precluded study of effects on hs-CRP with prolonged supplementation. Finally and importantly, although hs-CRP itself has been linked to risk of cardiovascular events, this study did not evaluate the clinical effect that the replacement of vitamin D would have directly on cardiovascular risk reduction via other mechanisms.

It is noteworthy that 43% of the eligible participants who had their initial screening blood drawn for this study met laboratory criteria for vitamin D insufficiency or deficiency. This suggests that lower blood levels of vitamin D appear to be common even among residents of “sunny Southern California.” In any case, the clinical significance of hypovitaminosis D in cardiac disease remains unclear.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgment

Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance.

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Figure 1. Log-transformed high-sensitivity C-reactive protein (hs-CRP) levels (mg/L) before and after vitamin D treatment.

Figure 2. Nearly significant correlation of pre-25-OH-vitamin D and post high-sensitivity C-reactive protein level.