Serum Calcitriol Concentrations and Kidney Function Decline, Heart Failure, and Mortality in Elderly Community-Living Adults: The Health, Aging, and Body Composition Study

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Rationale & Objectives: Lower 25-hydroxyvitamin D concentrations have been associated with risk for kidney function decline, heart failure, and mortality. However, 25-hydroxyvitamin D requires conversion to its active metabolite, calcitriol, for most biological effects. The associations of calcitriol concentrations with clinical events have not been well explored.

Study Design: Case-cohort study.

Setting & Participants: Well-functioning community-living older adults aged 70 to 79 years at inception who participated in the Health, Aging, and Body Composition (Health ABC) Study.

Predictor: Serum calcitriol measured using positive ion electrospray ionization-tandem mass spectrometry.

Outcomes: Major kidney function decline (≥30% decline in estimated glomerular filtration rate from baseline), incident heart failure (HF), and all-cause mortality during 10 years of follow-up.

Analytic Approach: Baseline calcitriol concentrations were measured in a random subcohort of 479 participants and also in cases with major kidney function decline [n = 397]) and incident HF (n = 207) during 10 years of follow-up. Associations of serum calcitriol concentrations with these end points were evaluated using weighted Cox regression to account for the case-cohort design, while associations with mortality were assessed in the subcohort alone using unweighted Cox regression.

Results: During 8.6 years of mean follow-up, 212 (44%) subcohort participants died. In fully adjusted models, each 1–standard deviation lower calcitriol concentration was associated with 30% higher risk for major kidney function decline (95% CI, 1.03-1.65; $P = 0.03$). Calcitriol was not significantly associated with incident HF (HR, 1.16; 95% CI, 0.94-1.47) or mortality (HR, 1.01; 95% CI, 0.81-1.26). We observed no significant interactions between calcitriol concentrations and chronic kidney disease status, baseline intact parathyroid or fibroblast factor 23 concentrations.

Limitations: Observational study design, calcitriol measurements at a single time point, selective study population of older adults only of white or black race.

Conclusions: Lower calcitriol concentrations are independently associated with kidney function decline in community-living older adults. Future studies will be needed to clarify whether these associations reflect lower calcitriol concentrations resulting from abnormal kidney tubule dysfunction or direct mechanisms relating lower calcitriol concentrations to more rapid loss of kidney function.

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Kidney function decline and incident heart failure (HF) are often-linked health conditions. Both are highly prevalent in older persons, and each is associated with high morbidity and mortality.[1,2] Multiple studies have reported that lower 25-hydroxyvitamin D concentrations are associated with progression of chronic kidney disease (CKD),[3,4] HF,[5-8] and mortality[9-13] in addition to key risk factors for these diseases, including diabetes, higher blood pressure, and inflammation.[14-19]

Prior studies have relied on measurements of serum 25-hydroxyvitamin D when evaluating relationships of vitamin D status with health outcomes. However, 25-hydroxyvitamin D is thought to be largely inactive because it requires conversion to the active hormone 1,25-dihydroxyvitamin D, also known as calcitriol. Calcitriol is produced by the kidney and extrarenal tissues that express 1α-hydroxylase.[20,21] The reliance on 25-hydroxyvitamin D measurements in prior studies is primarily due to 25-hydroxyvitamin D having a longer half-life and higher concentration than calcitriol, thus requiring less sample volume for reliable measurements. However, this approach may be flawed in situations that alter 1 α-hydroxylase activity, such as among persons with CKD or persons with alterations in parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23) concentrations because both these hormones regulate 1α-hydroxylase activity.[22,23] Also, routine tests used for measuring 25-hydroxyvitamin D measure the total circulating 25-hydroxyvitamin D concentration, not only the bioavailable free form, and this has been shown to lead to misinterpretation of vitamin D status in persons with genetic polymorphism in the vitamin D–binding protein

gene.[24] Moreover, vitamin D–binding protein concentrations may be decreased by obesity and insulin resistance, and thus vitamin D status may appear artificially lower in these conditions.[25,26]

Few prior studies have assessed whether calcitriol concentrations are associated with clinically relevant outcomes. The existing studies evaluated populations with prevalent chronic diseases, including advanced CKD[11,27,28] or coronary heart disease.[12,29] Thus, knowledge of the relationship of calcitriol concentrations with health outcomes in community-living populations is limited. Moreover, whether these relationships differ in persons with CKD and those with high or low PTH or FGF-23 concentrations remain unexplored.

The ratio of 24,25-dihydroxyvitmain D to 25-hydroxyvitamin D (the vitamin D metabolite ratio [VMR]) has been proposed as an another surrogate to calcitriol measurement.[30] Higher VMR is proposed to represent greater calcitriol concentrations and vitamin D receptor activity. It is not limited by vitamin D–binding protein concentrations because it would affect the ratio's numerator and the denominator similarly and cancel out in the calculation of VMR.[31] Additionally, components of the VMR circulate for longer and at higher concentrations than calcitriol, making routine measurement easier. No prior studies have evaluated whether the VMR is associated with renal or HF outcomes or compared these associations with those with calcitriol.

We evaluated associations of calcitriol concentrations and VMR with major kidney function decline, incident HF, and death in a cohort of well-functioning community-living older adults who participated in the Health, Aging, and Body Composition (Health ABC) Study. A priori, we hypothesized that lower calcitriol concentrations would independently be associated with kidney function decline, incident HF, and death.

Methods

Study Population

The Health ABC Study is a longitudinal cohort study designed to assess the health impact of changes in weight and body composition in older age. The study recruited 3,075 participants who were community dwelling, well functioning, and aged 70 to 79 years at inception between April 1997 and June 1998 from 2 study sites in Pittsburgh, PA, and Memphis, TN. Eligibility criteria included plans to remain in the geographic area for 3 or more years, absence of life-threatening illnesses, and self-reported ability to walk one-fourth of a mile, climb 10 steps, and perform basic activities of daily living without difficulty. All participants provided informed consent, and the Health ABC Study was approved by institutional review boards at the University of Tennessee Health Science Center and the University of Pittsburgh. In addition, the present study was approved by the institutional review board at University of California San Diego.

We used a case-cohort design for this study. Calcitriol measurements were made at the year-2 follow-up visit, so we selected this visit as our baseline visit. A priori, we randomly selected a subcohort of 500 participants from the parent Health ABC Study because our power calculations suggested that this would be adequate to address our aims. Among these, 21 had missing blood specimens, leading to 479 participants included in our analyses (Fig 1). We also selected cases with major kidney function decline, defined as ≥30% decline in estimated glomerular filtration rate (eGFR) during follow-up. We identified all 397 cases with major kidney function decline, of whom 77 arose within the subcohort and 320 were sampled outside the subcohort. For the incident HF end point, we excluded 15 participants with prevalent HF from the subcohort, leaving 464 participants for analysis. We then sampled a subset of 207 incident HF cases during follow-up, among whom 94 arose within the subcohort and 113 cases arose from the rest of the parent study. We evaluated all-cause mortality only within the random subcohort (212 cases) and did not supplement with additional mortality cases that occurred in the cohort outside the randomly selected subcohort (N = 737 deaths) for this more common end point, thus using a standard prospective cohort approach for this end point.

Vitamin D Measurements

Serum calcitriol was the primary predictor for our analysis. Calcitriol was measured using positive ion electrospray ionization-tandem mass spectrometry (Waters Xevo mass spectrometer; Waters Corp).[30] The reference interval was conducted using 40 specimens from healthy blood bank donors by analyzing specimens over multiple days and using nonparametric analysis for determination of the central 95% of the data.[3] The reference interval established for total 1,25-dihydroxyvitamin D was 19 to 67 pg/mL.[32] Limits of detection and quantification were 0.41 and 0.82 pg/mL, respectively.[33] Calcitriol intra- and interassay

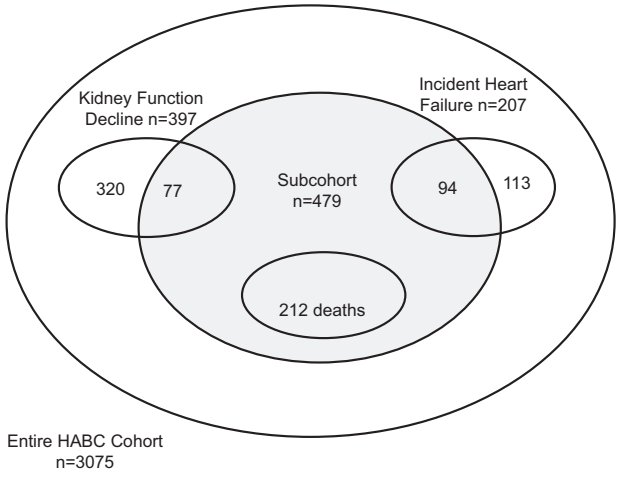

Figure 1. Study design. Abbreviation: HABC, Health, Aging, and Body Composition Study.