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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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Abstract

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.

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Authors' Contributions: Study concept and design: MJS, MGS, JHI; acquisition of data and statistical analysis: SBK, ANH, AN, MJS, MGS, JHI, RK; analysis and interpretation of data: US, RK, CG, MJS, MGS, JHI. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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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.

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 1α-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 coefficients of variation were 5.6% and 8.0% and 8.7 and 13%, respectively.[34] Serum 25-hydroxyvitamin D and 24,25 dihydroxyvitamin D were measured using liquid-liquid extraction and subsequent liquid chromatography-tandem mass spectrometry. VMR was a secondary predictor in our analysis. VMR was calculated by dividing serum 24,25-dihydroxyvitamin D_3 by serum 25-hydroxyvitamin D_3 and then multiplying by 100.[30,31] Because there is no spectroscopic evidence of 24,25-dihydroxyvitamin D_2, the VMR was calculated using 24,25-dihydroxyvitamin D_3 and 25-hydroxyvitamin D_3 only.

Outcomes

Mean follow-up was 6.4 years for major kidney function decline, 9.8 years for incident HF, and 8.6 years for all-cause mortality. A 30% decline in eGFR has recently been associated with adverse outcomes and recommended as an alternative end point for CKD progression.[33] eGFR assessments were available at years 1, 3, and 10, so we carried year-1 eGFRs to year 2, which was our baseline visit for this study. We defined major kidney function decline as ≥30% decline in eGFR from the year-1 visit to year 3 or year 10. We estimated GFR using the 2012 CKD Epidemiology Collaboration (CKD-EPI) cystatin C equation.[34]

Cystatin C was measured at the Health ABC core laboratory (University of Vermont, Burlington, VT) with a BNII nephelometer (Dade Behring Inc) that used a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Dade Behring Inc). The assay range for cystatin C was 0.195 to 7.330 mg/L, and long-term stability of the measurements has been previously shown with an intraindividual coefficient of variation of 7.7% among 61 healthy individuals with 3 cystatin C measurements over a 6-month period.[35] We elected to use serial measurements of cystatin C rather than creatinine because available creatinine measurements in the Health ABC Study were not isotope-dilution mass spectrometry (IDMS) standardized at baseline, but were IDMS standardized at the year-3 and −10 follow-up visits, which may introduce bias for the 30% decline end point.

Medical records for all overnight hospitalizations were collected and were adjudicated for HF events using prespecified criteria. Adjudication criteria for HF required: (1) physician diagnosis of congestive heart failure and treatment with a diuretic plus digitalis or a vasodilator drug (nitroglycerine, apresoline, or angiotensin-converting enzyme inhibitor), (2) cardiomegaly and pulmonary edema on chest radiograph, or (3) evidence of a dilated ventricle and global or segmental wall motion abnormalities with decreased systolic function by either echocardiography or contrast ventriculography. The Health ABC Study Diagnosis and Disease Ascertainment Committee reviewed all hospital records, death certificates, and informant interviews.

Other Measurements

All participants provided a medical history and went through physical activity assessments, physical examinations, and radiographic tests. Age, sex, race, education, and smoking status were determined by self-report. Height was measured using a Harpenden stadiometer (Holtain Ltd), and weight was measured using a balance beam scale. Body mass index was calculated in kg/m^2. Prevalent diabetes was defined using self-reported history, use of antidiabetic agents, fasting plasma glucose concentration ≥ 126 mg/dL, or a 2-hour oral glucose tolerance test result ≥ 200 mg/dL. Systolic and diastolic blood pressures were measured 3 times using a conventional mercury sphygmomanometer. Participants brought their medications to the study visits and study staff categorized them using the Iowa Drug Information System. Prevalent HF was defined by self-reported history of heart failure, use of selected medications, and *International Classification of Diseases, Ninth Revision, Clinical Modification* codes defined by the Centers for Medicare & Medicaid Services from 1995 to 1998.

Urine albumin and urine creatinine measurements were available only at year 1, so we carried forward the year-1 urine albumin-creatinine ratio (ACR) to year 2, which was our baseline visit for this study. Urine albumin was measured using a particle-enhanced turbidimetric inhibition immunoassay allowing for direct albumin quantification (Siemens). Urine creatinine was measured using a modified Jaffé method on a clinical chemistry analyzer (Siemens). Total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured in fasting serum using a colorimetric analyzer (Vitros 950; Johnson & Johnson), and low-density lipoprotein cholesterol was calculated using the Friedewald equation.[36] Serum calcium and phosphate were measured using direct quantitative

colorimetric determination (Stanbio Laboratory). Intact PTH (iPTH) was measured in EDTA serum using a 2-site immunoradiometric assay kit (N-tact PTHSP; DiaSorin). FGF-23 was measured using an intact assay (Kainos Laboratories).

Statistical Analysis

We evaluated the distribution of demographics and risk factors across calcitriol quartiles within the randomly selected subcohort. For the major kidney function decline and incident HF outcomes, we evaluated associations with time to event using modified Cox regression.[37] Subcohort participants were weighted by the inverse of their sampling fraction. Cases arising outside the sub-cohort were not weighted until the time of failure. All cases, irrespective of sampling in the subcohort or separately, were assigned a weight of 1 at the time of failure. The sampling fraction of noncases for major kidney function decline and incident HF was 402/2,678 = 0.15 and 370/2,774 = 0.13, respectively. We used robust variance estimators to accommodate the study design. For all-cause mortality, we implemented our analysis solely within the subcohort and as a result used standard Cox proportional hazards models without weights to generate hazard ratios.

We evaluated the associations with each outcome by quartiles of calcitriol and the VMR to assess linearity. We also evaluated calcitriol concentration and VMR as a continuous variables (per 1 standard deviation [SD] lower). We used sequential models. The first model adjusted for age, sex, race, and clinical center site. The second model added baseline eGFR and urine ACR. The third model additionally included prevalent diabetes, prevalent HF, smoking, systolic blood pressure, blood pressure medication use, and calcium, phosphate, iPTH, FGF-23, and 25-hydroxyvitamin D concentrations. For the incident HF outcome, prevalent cases of HF were excluded. In parallel, we used the same models to assess associations of 25-hydroxyvitamin D with the 3 outcomes and compared the strengths of associations of 25-hydroxyvitamin D versus calcitriol with each outcome in the fully adjusted model. For each clinical outcome, we assessed interactions by CKD status (eGFR ≥ 60 or <60 mL/min/1.73 m^2 at baseline), iPTH concentrations (stratified above or below the median [32 pg/mL]), and FGF-23 concentrations (stratified above or below the median [45 pg/mL]). All analyses were conducted using SPSS (IBM Corp; released 2013; version 22.0) and R (R Foundation for Statistical Computing). $P < 0.05$ was considered statistically significant for all analyses including interaction terms.

Results

Participant Characteristics

Among the 479 participants randomly selected for the subcohort, mean age was 74 ± 3 years, 52% were men, and 61% were white. Mean 25-hydroxyvitamin D concentration was 21.5 ± 10.3 ng/mL, mean calcitriol concentration was 40.6 ± 16.3 pg/mL, mean VMR was 4.81 ± 1.96, and mean eGFR was 73 ± 18 mL/min/1.73 m^2. Baseline characteristics by quartiles of calcitriol within the subcohort are shown in Table 1. Compared with participants with calcitriol concentrations in the highest quartile (>52 pg/mL), those in the lowest quartile (<34 pg/mL) were more likely to be men, white, and more educated. They were also more likely to have diabetes and to smoke, but were less likely to be hypertensive. They had

lower total and high-density lipoprotein cholesterol concentrations, but higher triglyceride concentrations. The lowest calcitriol quartile also had lower eGFRs and serum calcium and iPTH concentrations. FGF-23 concentrations were higher in the lowest quartile of calcitriol, whereas phosphate concentrations were similar across quartiles.

Associations of Serum Calcitriol Concentrations With Major Kidney Function Decline, Incident HF, and All-Cause Mortality

Associations of serum calcitriol concentrations with major kidney function decline, incident HF, and all-cause mortality are shown in Table 2. During a mean 6.4 years of follow-up, 397 participants from the entire Health ABC cohort had major kidney function decline. In the first model, each 1-SD lower calcitriol concentration was associated with 38% higher risk for major kidney function decline. Persons in the lowest quartile were at 83% higher risk for kidney function decline compared to the highest quartile in the first model, and the risk appeared to increase in persons with calcitriol concentrations below the median (<42 pg/mL). In the fully adjusted final model, the association of each 1-SD lower calcitriol concentration with major kidney function decline was only minimally attenuated from 38% in model 1 to 30% in model 3. In sensitivity analysis, we evaluated 40% and 50% eGFR decline outcomes. Associations were similar in direction and magnitude, but event rates were lower (204 and 91 for 40% and 50% eGFR decline, respectively).

We sampled 207 cases of incident HF during follow-up. Each 1-SD lower calcitriol concentration was associated with 42% higher risk for HF in the first model. Further adjustments for eGFR and urine ACR attenuated the association somewhat, but each 1-SD lower calcitriol concentration remained associated with 28% higher risk for HF. However, in the fully adjusted model, associations were further attenuated and were no longer statistically signifi-cant ($P = 0.2$).

Next, we evaluated the association of calcitriol concentration with all-cause mortality using standard prospective cohort analysis within the 479-person subcohort. In the first model, each 1-SD lower calcitriol concentration was associated with 22% higher risk for mortality, and there was a graded relationship of higher risk with sequentially lower calcitriol quartiles. However, adjustments for eGFR and urine ACR rendered the association no longer statistically significant ($P = 0.1$). In the fully adjusted model, associations were further attenuated and fully extinguished ($P = 0.9$).

Associations of VMR With Major Kidney Function Decline, Incident HF, and All-Cause Mortality

Associations of VMR with major kidney function decline, incident HF, and all-cause mortality are shown in Table 3. In the first model, each 1-SD lower VMR was associated with 28% higher risk for major kidney function decline, 24% higher risk for incident HF, and 18% higher risk for all-cause mortality. The associations with kidney function decline and HF attenuated by adjustment for eGFR and ACR and were no longer statistically significant in the fully adjusted model. However, the association of VMR with all-cause mortality remained significant, such that each 1-SD lower VMR was associated with 19% higher risk for all-cause mortality.

Comparison of Associations of 25-Hydroxyvitamin D With Major Kidney Function Decline, Incident HF, and All-Cause Mortality in Fully Adjusted Models

In fully adjusted models, we did not observe statistically significant associations of 25-hydroxyvitamin D levels with any of the clinical end points (Table S1). Each 1-SD lower 25-hydroxyvitamin D concentration was associated with 12% higher risk for major kidney function decline, compared with 30% higher risk that we observed for each 1-SD lower calcitriol concentration (Fig 2).

Interactions of Associations by CKD Status and PTH and FGF-23 Concentrations

We evaluated whether the associations of calcitriol concentration or VMR with each of the 3 outcomes differed by baseline CKD status and among persons who had iPTH or FGF-23 concentrations above versus below the median. We did not observe statistically significant interactions (all P for interactions > 0.1; Table S2). Similar to results with calcitriol concentrations, we did not observe statistically significant interactions by CKD, PTH, or FGF-23 strata when evaluating 25-hydroxyvitamin D or VMR (Tables S3 and S4).

Discussion

In this study we evaluated associations of serum calcitriol concentrations with clinical outcomes in community-living older adults. We observed that lower calcitriol concentrations were independently associated with risk for major kidney function decline, an association that was stronger than that of 25-hydroxyvitamin D level with the same outcome. Lower calcitriol concentrations were not associated with incident HF or all-cause mortality in fully adjusted models. CKD, PTH, and FGF-23 are all known to influence calcitriol production, so we investigated whether relationships differed in subgroups defined by these variables. In all cases, associations were similar irrespective of CKD status or higher versus lower iPTH and FGF-23 levels.

Although a number of studies have evaluated associations of 25-hydroxyvitamin D concentrations with relevant clinical outcomes, only a few have evaluated similar associations with the biologically active hormone calcitriol. The activity of 1α-hydroxylase, which converts 25-hydroxyvitamin D to calcitriol, is affected by kidney function, FGF-23, and PTH. FGF-23 is a potent inhibitor of 1α-hydroxylase,[38] whereas PTH is a 1α-hydroxylase activator.[39] Therefore, we hypothesized that 25-hydroxyvitamin D concentrations may not always accurately reflect calcitriol concentrations, particularly in the setting of CKD or other clinical situations that alter FGF-23 and PTH metabolism. In our study, the relationship of calcitriol with each of the 3 outcomes was similar by CKD status and among persons with iPTH and FGF-23 concentrations above versus below the median. Interestingly, the relationship of 25-hydroxyvitamin D with these outcomes was also similar by CKD status and among persons with iPTH and FGF-23 concentrations above versus below the median. However, the associations observed with calcitriol were stronger than that of 25-hydroxyvitamin D, which raises questions of the utility of assessing vitamin D activity using 25-hydroxyvitamin D alone.

To our knowledge, only 2 prior studies have evaluated the association of calcitriol concentration with longitudinal kidney function decline. Kendrick et al[27] assessed associations of both 25-hydroxyvitamin D and calcitriol concentrations with time to initiation of dialysis therapy in patients with advanced CKD. Similar to our findings, they observed that lower calcitriol concentrations were associated with progression to dialysis therapy, whereas there were no associations between lower 25-hyroxyvitamin-D concentrations with dialysis therapy risk.[27] However, participants in their study had a mean eGFR of 18 ± 7 mL/min/1.73 m^2 at baseline, whereas ours largely had preserved kidney function (mean eGFR, 73 ± 18 mL/min/1.73 m^2). In another study, Ravani et al[28] evaluated associations of both plasma 25-hydroxyvitamin D and calcitriol concentrations with CKD progression. They studied 168 new referrals to a CKD clinic with a mean eGFR of 34 ± 17 mL/min/1.73 m^2 at baseline and reported no association of calcitriol concentrations with CKD progression, whereas 25-hydroxyvitamin D concentrations was associated with progression to dialysis therapy.[28] Whether the conflicting results in the Ravani et al study relative to the Kendrick et al study and ours reflect smaller sample size, study population characteristics, or measurement techniques is unknown. Thus, we confirm the findings by Kendrick et al that lower calcitriol concentrations are associated with longitudinal decline in kidney function, independent of baseline eGFR or urine ACR. We also meaningfully extend the body of knowledge by demonstrating that the relationship is evident in community-living older persons with relatively preserved kidney functions at baseline.

What mechanisms may link lower calcitriol concentrations with progressive kidney function decline? We believe that lower calcitriol concentrations may reflect nonglomerular aspects of kidney function. In the course of kidney disease, several mechanisms account for decreased circulating calcitriol. First, reduction in functioning kidney mass may limit the kidney's ability to convert 25-hydroxyvitamin D to calcitriol. Second, reduction in GFR may limit delivery of substrate to the 1α-hydroxylase enzyme.[40,41] Third, persons with CKD often have high FGF-23 concentrations, which may inhibit 1α-hydroxylase activity.[36] One or more of these factors may explain why persons with lower eGFRs had lower calcitriol concentrations at baseline in our study. Lower calcitriol concentrations were also associated with declines in kidney function longitudinally, even when adjusting for eGFR and albuminuria at baseline. Low calcitriol levels have been associated with hypertension, diabetes, and inflammation, which are all established risk factors for CKD progression. However, we adjusted for these variables and the association with progressive kidney function decline persisted. Because regulation of calcitriol production occurs in kidney tubules, lower calcitriol concentrations may reflect the health of the kidney tubules and their ability to generate calcitriol. Through this, lower calcitriol levels may serve as a marker of poor kidney tubule health above and beyond eGFR and urine ACR, which primarily reflect glomerular health, and this may explain the observed association with more rapid longitudinal decline in kidney function seen here.

There is growing evidence that vitamin D deficiency plays a role in HF pathogenesis. The vitamin D receptor is expressed in endothelial cells, vascular smooth muscle cells, and cardiac myocytes. Li et al[42] demonstrated that vitamin D receptor knockout mice have significant over-production of renin, leading to hypertension, cardiac enlargement, and elevation of natriuretic peptide levels. In cardiac myocytes, calcitriol-dependent calcium-

binding protein and calcitriol-mediated voltage-dependent calcium channels exist, suggesting a potential role of calcitriol in myocardial contractility.[43] We therefore evaluated the association of calcitriol concentration with incident HF. Although we observed that lower calcitriol concentrations were associated with HF risk in unadjusted and demographic-adjusted models, fully adjusted models attenuated the association and rendered it no longer statistically significant. Whether this was a consequence of insufficient statistical power or lack of biological effect is uncertain, and results should be interpreted within the context of the 95% confidence intervals. Future studies with larger sample sizes are required to further evaluate this important question.

A few prior studies have evaluated the association of calcitriol with all-cause mortality in various clinical settings. Two studies reported that lower calcitriol concentrations are associated with mortality in patients with very advanced CKD.[11,27] Two other studies found that lower calcitriol concentrations were associated with mortality in patients with prevalent cardiovascular disease.[12,29] We evaluated the association of calcitriol concentration with all-cause mortality in community-dwelling older adults. We found no association of calcitriol with mortality risk.

We know of no prior studies that assessed the associations of VMR with any of the outcomes we evaluated. Although the association between VMR and major kidney function decline was not statistically significant in fully adjusted models, the associations were suggestive of a potential effect. We found that lower VMR was associated with higher risk for all-cause mortality. Considering that calcitriol concentrations were not associated with all-cause mortality, this raises the question of whether VMR is indicative of something other than calcitriol concentration or if calcitriol measurement is limited by fluctuations due to a short half-life, while the VMR is not. We suggest that additional studies evaluating VMR as a predictor of these outcomes in larger study samples would be valuable before using VMR as a clinical surrogate of calcitriol activity.

One strength of our study is the availability of calcitriol measurements using tandem mass spectrometry. Although a few observational studies have evaluated associations of calcitriol concentrations with clinical end points, all prior studies have to our knowledge relied on immunoassay-based methods. Immunoassay methods can lead to less accurate and less specific measurements due to lack of concordance across platforms, autoantibodies, antireagent antibodies, and the high-dose hook effect compared to tandem mass spectrometry.[44] Other strengths of our study include large numbers of clinically relevant outcomes, representation of both sexes from the community in multiple sites, and availability of information for possible cofounders such as demographics, hypertension, diabetes, prevalent HF, smoking, medication use, and FGF-23 and iPTH measurements.

This study also has important limitations. First, as an observational study, we are unable to ascribe cause-effect relationships. Second, participants were aged 70 to 79 years and of black or white race. Whether our results generalize to younger populations or other races/ethnicities remains uncertain. Third, as summarized previously, prior studies have found associations of calcitriol concentrations with HF and mortality in prevalent disease cohorts, while we did not. Whether discrepant results reflect differences in study populations,

measurements, or statistical power is uncertain and requires additional study. Next, calcitriol measurements were made at a single time point. Considering the short half-life of calcitriol, studies with multiple calcitriol measurements would be valuable. Whether longitudinal changes in calcitriol concentrations may be associated with outcomes is uncertain. For the major kidney function decline end point, participants needed to survive and return for follow-up eGFR assessment, by necessity. Thus, whether persons who died during follow-up or were too sick to return to follow-up visits may have introduced bias is a possibility. The lack of association of calcitriol level with mortality makes this less likely.

In community-dwelling older adults with preserved kidney function, lower calcitriol concentrations are independently associated with major kidney function decline. If these findings are confirmed, future studies should determine whether serum calcitriol measurement provides a surrogate for kidney tubule function and may facilitate assessment of nonglomerular aspects of kidney health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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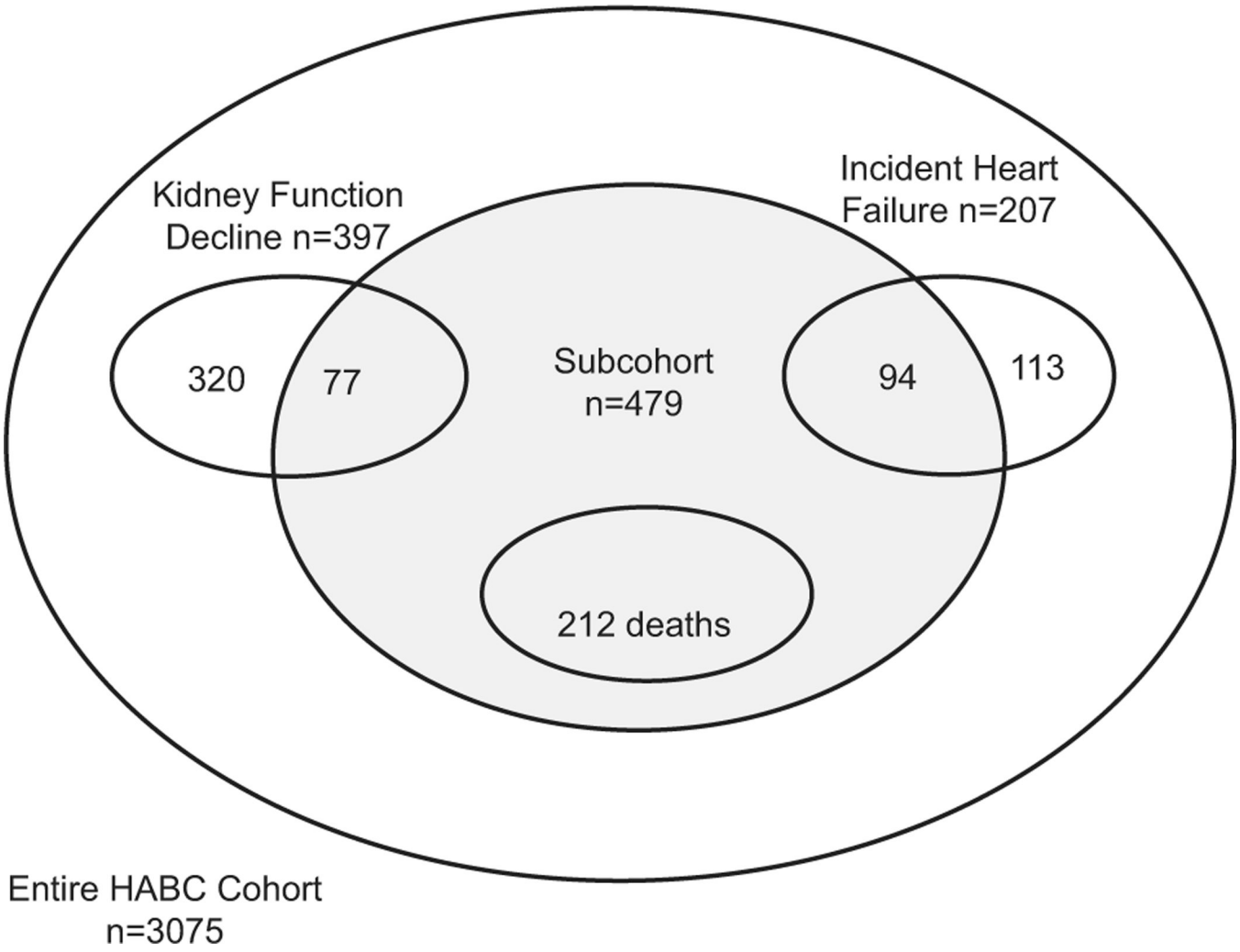

Figure 1.
Study design. Abbreviation: HABC, Health, Aging, and Body Composition Study.

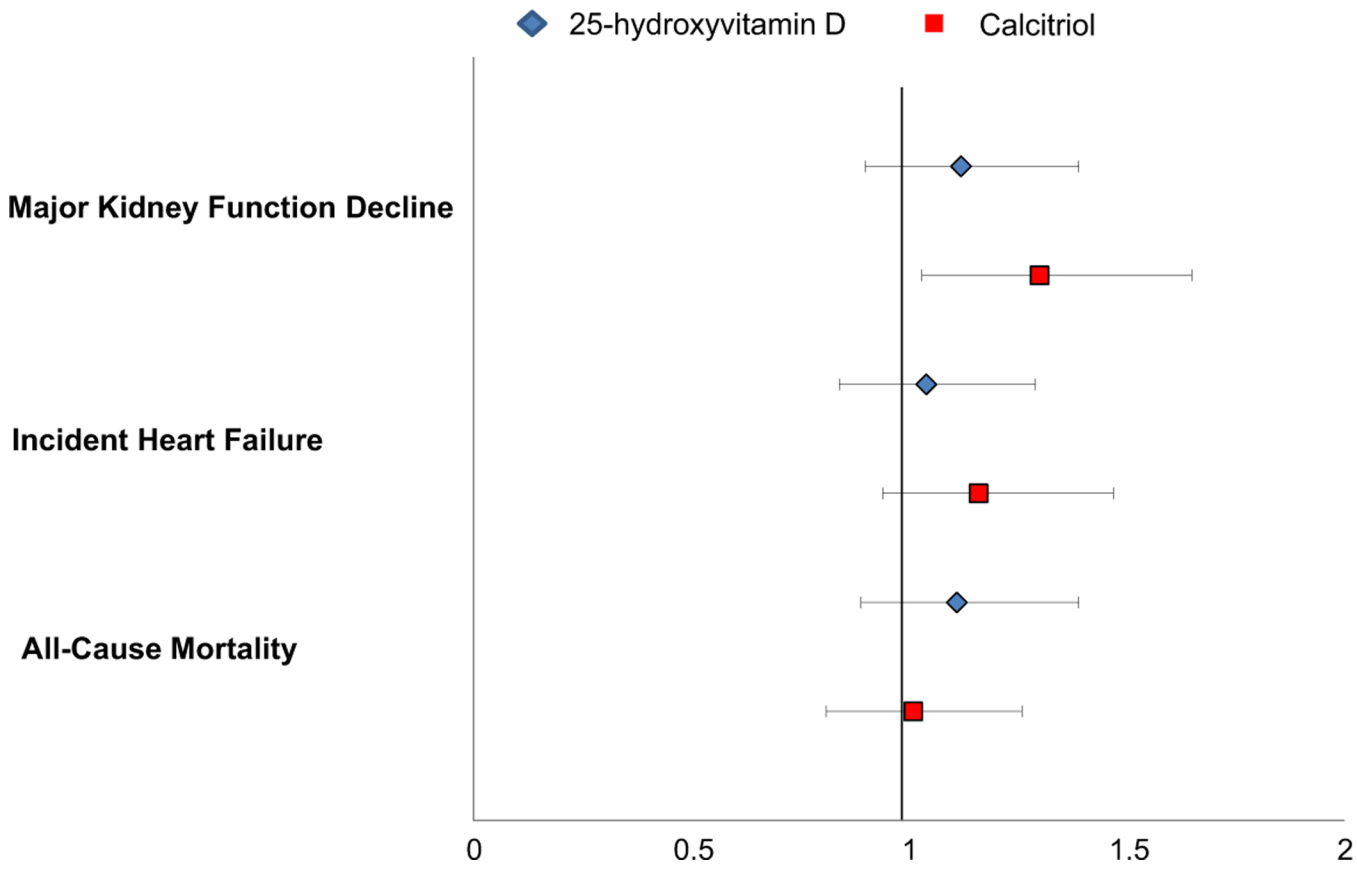

Figure 2.
Hazard ratio of 1 standard deviation lower 25-hydroxyvitamin D concentration versus calcitriol with clinical end points in the elderly.

Table 1.

Baseline Characteristics of Study Participants by Calcitriol Quartiles Within the Subcohort

No. of participants	Q1 (<34.46 pg/mL) n = 120	Q2 (34.46–41.81 pg/dL) n = 120	Q3 (41.82–52.14 pg/mL) n = 120	Q4 (>52.14 pg/mL) n = 119
Age, y	74 ± 3	74 ± 3	74 ± 3	73 ± 3
Male sex	75 (63%)	59 (49%)	64 (53%)	49 (41%)
White	96 (80%)	75 (63%)	70 (58%)	53 (45%)
Black	24 (20%)	45 (38%)	50 (42%)	66 (56%)
Education				
<High school	24 (20%)	18 (15%)	27 (23%)	36 (31%)
High school	33 (28%)	45 (38%)	50 (42%)	66 (56%)
Postsecondary	62 (52%)	56 (47%)	56 (47%)	33 (28%)
Hypertension	57 (48%)	61 (51%)	61 (52%)	71 (60%)
Diabetes mellitus	25 (21%)	19 (16%)	22 (18%)	11 (9%)
Smoking status				
Current	66 (55%)	59 (49%)	63 (53%)	57 (48%)
Former	9 (8%)	14 (12%)	7 (6%)	9 (8%)
Never	45 (38%)	47 (39%)	50 (42%)	53 (45%)
Use of statin	20 (17%)	16 (13%)	12 (10%)	15 (13%)
Body mass index, kg/m^2	27.0 ± 4.1	27.5 ± 5.0	27.0 ± 4.2	27.3 ± 4.6
Systolic BP, mm Hg	134 ± 22	134 ± 20	132 ± 19	136 ± 23
Diastolic BP, mm Hg	69 ± 12	69 ± 12	72 ± 11	72 ± 11
Total cholesterol, mg/dL	192 ± 35	203 ± 39	199 ± 38	208 ± 38
HDL cholesterol, mg/dL	48 ± 15	54 ± 17	53 ± 17	57 ± 17
LDL cholesterol, mg/dL	114 ± 31	122 ± 33	118 ± 35	125 ± 37
Triglycerides, mg/dL	133 [103, 166]	119 [87, 169]	126 [87, 174]	109 [85, 150]
Serum calcium, mg/dL	8.78 ± 0.44	8.74 ± 0.46	8.86 ± 0.35	8.84 ± 0.39
25-Hydroxyvitamin D, ng/mL	27 ± 14	23 ± 10	24 ± 10	23 ± 10
24,25-Dihydroxyvitamin D, ng/mL	2.53 ± 1.70	2.16 ± 1.49	2.28 ± 1.58	2.03 ± 1.51
VMR	5.36 ± 1.98	4.87 ± 2.22	4.73 ± 1.72	4.27 ± 1.75

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No. of participants	Q1 (<34.46 pg/mL) n = 120	Q2 (34.46–41.81 pg/dL) n = 120	Q3 (41.82–52.14 pg/mL) n = 120	Q4 (>52.14 pg/mL) n = 119
Vitamin D supplementation	18 (15%)	12 (10%)	10 (8%)	6 (5%)
PTH, pg/mL	30 [24, 39]	31 [24, 40]	34 [25, 44]	36 [26, 49]
FGF-23, pg/mL	54 [42, 70]	45 [36, 54]	40 [31, 51]	35 [27, 45]
Serum phosphorus, mg/dL	3.54 ± 0.53	3.61 ± 0.51	3.49 ± 0.46	3.53 ± 0.51
eGFR, mL/min/1.73 m^2	67 ± 19	73 ± 18	75 ± 17	78 ± 16
eGFR < 60 mL/min/1.73 m^2	40 (33%)	29 (24%)	23 (19%)	12 (10%)
Urine ACR ≥ 30 mg/g	28 (23%)	18 (15%)	25 (21%)	21 (18%)
Urine ACR, mg/g	7.4 [4.9, 27.7]	8.4 [4.5, 19.1]	7.9 [4.1, 18.6]	8.2 [5.1, 17.0]

Values for continuous variables given as mean ± standard deviation or median [Q1, Q3]; values for categorical variables, as count (percentage).

Abbreviations: ACR, albumin-creatinine ratio; BP, blood pressure; eGFR, estimated glomerular filtration rate (based on cystatin C); FGF-23, fibroblast growth factor 23; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PTH, parathyroid hormone; Q, quartile; VMR, vitamin D metabolite ratio.

Table 2.

Associations of Serum Calcitriol Concentrations With Major Kidney Function Decline, Incident Heart Failure, and All-Cause Mortality in Community-Living Individuals in the Health ABC Study

	No. of Participants	No. of Events	Model 1		Model 2		Model 3	
			HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Major Kidney Function Decline								
Continuous: per 1-SD lower calcitriol	799	397	1.38 (1.13–1.67)	0.001	1.33 (1.09–1.63)	0.005	1.30 (1.03–1.65)	0.02
Categorical: per calcitriol quartile								
Q1	217	118	1.83 (1.09–3.08)		1.61 (0.94–2.75)		1.50 (0.84–2.69)	
Q2	192	96	1.41 (0.87–2.29)		1.42 (0.87–2.31)		1.15 (0.65–2.05)	
Q3	190	87	0.88 (0.54–1.44)		0.81 (0.49–1.35)		0.88 (0.51–1.52)	
Q4	200	96	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Incident Heart Failure								
Continuous: per 1-SD lower calcitriol	557	207	1.42 (1.16–1.74)	0.001	1.28 (1.03–1.58)	0.02	1.16 (0.94–1.47)	0.2
Categorical: per calcitriol quartile								
Q1	152	66	2.21 (1.32–3.69)		1.63 (0.94–2.80)		1.31 (0.71–2.43)	
Q2	146	52	1.40 (0.84–2.31)		1.22 (0.72–2.06)		1.04 (0.58–1.86)	
Q3	141	50	1.43 (0.87–2.38)		1.17 (0.68–1.99)		1.29 (0.74–2.25)	
Q4	138	39	1.00 (reference)		1.00 (reference)		1.00 (reference)	
All-Cause Mortality								
Continuous: per 1-SD lower calcitriol	479	212	1.13 (0.97–1.30)	0.1	1.10 (0.95–1.28)	0.2	1.01 (0.85–1.20)	0.9
Categorical: per calcitriol quartile								
Q1	120	57	1.41 (0.94–2.13)		1.31 (0.86–1.99)		1.06 (0.67–1.69)	
Q2	120	53	1.25 (0.84–1.87)		1.25 (0.83–1.87)		1.08 (0.70–1.67)	
Q3	120	54	1.39 (0.93–2.08)		1.31 (0.88–1.97)		1.28 (0.85–1.94)	
Q4	119	48	1.00 (reference)		1.00 (reference)		1.00 (reference)	

Model 1: adjusted for age, sex, race, and site. Model 2: adjusted for model 1 variables plus estimated glomerular filtration rate and albumin-creatinine ratio. Model 3: adjusted for model 2 variables plus prevalent diabetes, prevalent heart failure, smoking, systolic blood pressure, blood pressure medication use, and calcium, phosphate, intact parathyroid hormone, fibroblast growth factor 23, and 25-hydroxyvitamin D concentrations.

Abbreviations: CI, confidence interval; Health ABC, Health, Aging, and Body Composition; HR, hazard ratio; Q, quartile; SD, standard deviation.

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Table 3.

Association of VMR With Risk for Kidney Function Decline, Incident HF, and Mortality

	No. of Participants	No. of Events	Model 1		Model 2		Model 3	
			HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Major Kidney Function Decline								
Continuous: per 1-SD lower VMR	799	397	1.28 (1.05–1.56)	0.02	1.22 (0.99–1.50)	0.06	1.21 (0.97–1.51)	0.1
Categorical: per VMR quartile								
Q1	241	121	1.78 (1.08–2.93)		1.63 (0.96–2.75)		1.50 (0.83–2.72)	
Q2	195	99	1.18 (0.73–1.92)		1.07 (0.63–1.80)		1.13 (0.64–2.00)	
Q3	192	87	1.03 (0.63–1.69)		1.05 (0.63–1.74)		1.23 (0.73–2.08)	
Q4	198	90	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Incident HF								
Continuous: per 1-SD lower VMR	577	207	1.24 (1.03–1.51)	0.03	1.07 (0.88–1.31)	0.5	1.01 (0.82–1.25)	0.9
Categorical: per VMR quartile								
Q1	147	67	1.77 (1.08–2.89)		1.26 (0.74–2.13)		0.99 (0.54–1.82)	
Q2	152	52	1.09 (0.67–1.79)		0.79 (0.47–1.35)		0.72 (0.41–1.27)	
Q3	139	44	0.94 (0.57–1.55)		0.90 (0.54–1.50)		0.94 (0.55–1.60)	
Q4	139	44	1.00 (reference)		1.00 (reference)		1.00 (reference)	
All-Cause Mortality								
Continuous: per 1-SD lower VMR	479	212	1.18 (1.02–1.38)	0.03	1.14 (0.99–1.33)	0.3	1.19 (1.01–1.41)	0.04
Categorical: per VMR quartile								
Q1	119	66	1.70 (1.15–2.53)		1.62 (1.09–2.42)		1.81 (1.17–2.78)	
Q2	120	55	1.45 (0.97–2.17)		1.39 (0.92–2.09)		1.46 (0.96–2.23)	
Q3	120	46	1.02 (0.67–1.54)		1.06 (0.70–1.61)		1.07 (0.70–1.65)	
Q4	120	45	1.00 (reference)		1.00 (reference)		1.00 (reference)	

Model 1: adjusted for age, sex, race, and site. Model 2: adjusted for model 1 variables plus estimated glomerular filtration rate and albumin-creatinine ratio. Model 3: adjusted for model 2 variables plus prevalent diabetes, prevalent heart failure, smoking, systolic blood pressure, blood pressure medication use, and calcium, phosphate, intact parathyroid hormone, fibroblast growth factor 23, and 25-hydroxyvitamin D concentrations.

Abbreviations: CI, confidence interval; HF, heart failure; HR, hazard ratio; SD, standard deviation; VMR, vitamin D metabolite ratio.