FGF23 Modifies the Relationship Between Vitamin D and Cardiac Remodeling

Bonnie Ky, MD, MSCE; Justine Shults, PhD; Martin G. Keane, MD; Martin St. John Sutton, MBBS; Myles Wolf, MD, MMSc; Harold I. Feldman, MD, MSCE; Peter P. Reese, MD, MSCE; Cheryl A. Anderson, PhD; Raymond R. Townsend, MD; Rajat Deo, MD; Joan Lo, MD; Crystal Gadegbeku, MD; Dean Carlow, MD, PhD; Michael J. Sulik, MA; Mary B. Leonard, MD, MSCE; and the CRIC Study Investigators*

Background—There is growing evidence to support an important role for vitamin D and related hormones, parathyroid hormone and fibroblast growth factor 23 (FGF23), on cardiac remodeling in chronic kidney disease. Our objective was to determine the relationships between vitamin D and cardiac remodeling in chronic kidney disease and the effects of parathyroid hormone and FGF23 on these associations.

Methods and Results—In 1,431 participants from the Chronic Renal Insufficiency Cohort study, we measured 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D (1,25(OH)2D), FGF23, and parathyroid hormone and performed quantitative echocardiography. Using linear regression methods, we determined significant negative interactions between 25(OH)D and FGF23 on left ventricular (LV) mass (P=0.016), end-diastolic volume (P=0.029), and end-systolic volumes (P=0.021). In participants with an FGF23 level greater than the median of 123.5 RU/mL, each doubling of 25(OH)D was associated with a 2.5% (95% confidence interval, −4.8, −0.2) lower LV mass. This association was less pronounced with FGF23 levels less than the median (0.4%; 95% confidence interval, −1.9, 2.7). Conversely, in participants with deficient 25(OH)D levels <20 ng/mL, each doubling of FGF23 was associated with a 3.4% (95% confidence interval, −1.2, 5.6) greater LV mass compared with only a 1.6% (95% confidence interval, −0.2, 3.5) difference in participants with sufficient 25(OH)D. Similar findings were observed with 25(OH)D and volumes (P<0.05), and 1,25(OH)2D and LV mass and volumes (P<0.005). There was no effect modification by parathyroid hormone.

Conclusions—We identified significant interactions among 25(OH)D, 1,25(OH)2D, and FGF23 on cardiac remodeling. Increased LV mass and cavity dilatation were observed with low 25(OH)D and high FGF23. Our findings suggest that consideration of both hormones is crucial to understanding the role of either in cardiac remodeling, and may have important therapeutic implications. (Circ Heart Fail. 2013;6:817-824.)

Key Words: cardiac remodeling • echocardiography • vitamin D

Vitamin D deficiency and related abnormalities in mineral metabolism are highly prevalent in chronic kidney disease (CKD).1 With advancing renal dysfunction, 25-hydroxyvitamin D (25(OH)D) deficiency and downregulation of the renal 1-α-hydroxylase result in impaired conversion of vitamin D (25(OH)D) to the active 1,25-dihydroxyvitamin D (1,25(OH)2D); abnormal mineral metabolism; and increases in parathyroid hormone (PTH). 1,25(OH)2D is further downregulated by fibroblast growth factor 23 (FGF23), the latter which is also markedly increased in renal failure.1,2

Clinical Perspective on p 824

There is a growing body of basic and clinical evidence that supports an important role for vitamin D metabolism in the maintenance of cardiovascular homeostasis. Animal studies demonstrate a protective effect of vitamin D against adverse cardiac remodeling.3 Vitamin D is a negative regulator of the renin–angiotensin system and acts to reduce hypertrophic gene expression.4 Mice lacking the vitamin D receptor have elevated production of renin and angiotensin II, resulting in...
hypertension and cardiac hypertrophy. Studies of a cardiomyocyte-specific genetic deletion of the vitamin D receptor suggest an increase in myocyte size and left ventricular hypertrophy (LVH) of the murine conditional knockout.

Epidemiologically, vitamin D deficiency is associated with renal disease, hypertension, heart failure, and adverse cardiovascular outcomes. Clinical studies demonstrate a relationship among vitamin D, blood pressure (BP), and renin activity. Furthermore, low 25(OH)D levels are associated with more advanced New York Heart Association Class heart failure and impaired LV function. Most recently, in 115 participants with CKD, although paricalcitol administration was not associated with a significant reduction in LV mass during a 48-week period, treated patients did demonstrate smaller increases in B-type natriuretic peptide, fewer cardiovascular events, and a reduction in atrial volume compared with controls, suggestive of an effect of vitamin D on cardiac remodeling.

Furthermore, recent studies have also demonstrated important effects of vitamin D–related markers of mineral metabolism on cardiac remodeling. In 2312 participants in the Cardiovascular Health Study, PTH levels ≥65 pg/mL were associated with a 30% greater risk for heart failure. Faul et al demonstrated a significant relationship between increased FGF23 levels and LVH in CKD that persisted after adjustment for 25(OH)D and defined a role for FGF23 in the development of pathological hypertrophy.

However, the interactions among these markers of mineral metabolism and cardiac remodeling, and the potential relationships between 25(OH)D and 1,25(OH)2D, and FGF23 and PTH, have not been comprehensively defined in CKD. We were specifically interested in the interaction by PTH and FGF23 on the association between 25(OH)D and 1,25(OH)2D, and LV mass and cardiac remodeling. We thus measured the following biomarkers: 25(OH)D, 1,25(OH)2D, FGF23, and PTH, in 1431 participants from the Chronic Renal Insufficiency Cohort (CRIC) study who had quantitative echocardiography measures of mass, volumes, and ejection fraction. Our objective was to determine the relationships between 25(OH)D and 1,25(OH)2D and echocardiographic parameters of cardiac size and function in a large, diverse CKD population, and define the potential effects of PTH and FGF23 on these associations. We hypothesized that FGF23 excess and vitamin D deficiency would exert multiplicative effects on increasing LV mass and hypertrophy.

Methods

Study Population

The CRIC study is a National Institutes of Health–sponsored/National Institute of Diabetes and Digestive and Kidney–sponsored, multicenter prospective cohort study established to study the progression of cardiovascular and renal disease among patients with CKD. Participants were recruited on the basis of age-related entry criteria for estimated glomerular filtration rate (eGFR). Exclusion criteria included life expectancy <3 years, New York Heart Association Class III or IV heart failure, known cirrhosis, HIV, prior end-stage renal disease, organ or bone marrow transplant, immunosuppressive therapy within the prior 6 months, chemotherapy within the past 2 years, polycystic kidney disease, pregnancy, and institutionalized patients. A total of 3612 individuals aged 21 to 74 years with an eGFR between 20 and 70 mL/min per 1.73 m2 were recruited between June 2003 and March 2007. Participants underwent extensive baseline and follow-up evaluations involving blood sampling and detailed questionnaires. All participants underwent 2-dimensional (2D) trans-thoracic echocardiograms at the year 1 visit.

These analyses used data from an ancillary vitamin D study, which was conducted at 4 of the 7 clinical centers of the CRIC study: University of Pennsylvania, University of Michigan, Kaiser/University of California at San Francisco, and Johns Hopkins University. In these participants, serum vitamin D and PTH levels were obtained at the year 1 visit concurrent with echocardiograms from participants representative of the clinical sites. FGF23 levels were obtained at baseline. The protocol was approved by the institutional review board at each site.

Vitamin D, PTH, and FGF23 Measurements

Serum 25(OH)D was measured using mass spectrometry, and 1,25(OH)2D was measured using an established 125I-labeled radioimmunoassay from banked, previously unthawed year 1 samples stored at −80°C. For 25(OH)D, the limit of quantitation was 1.3 ng/mL. The interassay coefficient of variation for 25(OH)D was 7.3% to 10.0% and for 1,25(OH)2D was 7% to 11%. Year 1 plasma iPTH (pg/mL) was quantified using a radioimmunoassay with 125I-labeled antibody (Scantibodies Clinical Laboratory, Santee, CA). The coefficient of variation for iPTH was 3% to 5%. FGF23 was measured in duplicate after a single thaw of stored baseline plasma samples using a second-generation C-terminal ELISA (Immunotopics) from baseline samples stored at −80°C. The coefficient of variation was 7.6%. Aldosterone was measured after a single thaw of stored baseline plasma samples using a commercially available ELISA (BioVendor). The coefficient of variation ranged from 6.5% to 8.7%.

Quantitative Echocardiography

Digital 2D transthoracic echocardiograms were analyzed on TomTec computer workstations (TomTec Imaging Systems, Unterschleissheim, Germany). Linear measurements of LV dimensions were performed in the parasternal long axis view using 2D echo and included LV internal dimension at end-diastole and end-systole. LV length at end-systole and end-diastole was obtained by measuring the distance from the apical endocardium to the center of the mitral valve plane in the 4-chamber view. LV mass was estimated at end-diastole by digitizing the endocardial and epicardial surfaces of the LV short axis to obtain short axis myocardial areas. LV mass (g) was calculated using the area–length method (5/6 short axis myocardial area×LV cavity length×myocardial density [1.055]). LV mass was indexed to height to the 2.7th power. The presence of LVH was identified using standard, sex-specific cut points: LV mass index ≥50 g/m2.7 in men or ≥47g/m2.7 in women. LV end-diastolic volume (EDV) and end-systolic volume ( ESV) were obtained using Simpson’s method of discs as recommended by the American Society of Echocardiography. LV volumes were indexed to height2.5. Ejection fraction was calculated from 2D LV volumes as (EDV–ESV)/EDV×100%.

Statistical Methods

The data were examined using summary statistics (percentiles, means, SD, medians with interquartile ranges denoting the 25th and 75th percentiles) and markers log-transformed when appropriate. In initial analyses, the univariate cross-sectional associations with clinical correlates at time of vitamin D measure were determined using χ2 test for categorical variables and t test for continuous variables. These included variables pertaining to demographics (age, sex, and race), social (tobacco and ethanol history), and medical history (cardiovascular disease, hypercholesterolemia, atrial fibrillation, hypertension, and diabetes mellitus); clinical measures (body mass index [BMI], BP, and eGFR using the CRIC equation); medical therapy (angiotensin-converting enzyme-inhibitor, angiotensin receptor blocker, and β-blocker); and season of blood draw. Univariable models were then generated using continuous (natural log transformed) and categorical forms of 25(OH)D and 1,25(OH)2D as predictors and echocardiographic parameters as the outcomes. We defined categories according to percentile distributions for both measures; for 25(OH)D, we also defined deficient versus not according
to the recent Institute of Medicine guideline definitions of <20 versus ≥20 ng/mL. We selected potential confounders for multivariable adjustment both on the basis of the univariable associations with vitamin D metabolite or cardiac remodeling parameter using a *P* value <0.05 as the significance level and clinical judgment. Model assumptions were verified using regression diagnostics, and lack of significant collinearity was also confirmed using the *vif* command after construction of the multivariable regression models.

In individual models, we investigated the possibility of effect modification by PTH and FGF23 on the association between 25(OH)D and echocardiographic measures of cardiac structure and function. We a priori hypothesized that the association between 25(OH)D and LV mass could differ according to PTH and FGF23 given the biological interactions between these mineral metabolites and 25(OH)D and 1,25(OH)D. We, therefore, included interaction terms (eg, 25(OH)D by FGF23) in the models to identify statistically significant interactions. To assess the difference in relationships, we present the results as the percent change in echocardiographic remodeling parameter for each doubling of biomarker (eg, 25(OH)D above and below the median level of the opposing marker (eg, FGF23). The parameters and biomarkers were natural log transformed, so that the percentage difference in the parameter of interest (with 95% confidence interval [CI]) associated with a doubling in the biomarker was estimated by $2^{\beta}$, where $\beta$ is the regression coefficient for natural log of the biomarker. The 95% CI were estimated by $(2^{\beta_{\text{lower}}}-1)\times100$ to $(2^{\beta_{\text{upper}}}-1)\times100$, where $\beta_{\text{lower}}$ and $\beta_{\text{upper}}$ were the lower and upper values of the 95% CI for $\beta$, respectively. Models with interaction terms allowed for the identification of significant interactions, whereas the estimation of the percentage difference in the parameter of interest with 95% CI in stratified analyses illustrated the nature of the potential interactions that supplemented our formal interaction testing. A similar approach was taken for models whereby we examined the effects of doubling FGF23 above and below the median level of 25(OH)D or 1,25(OH)D. All analyses were performed using STATA 12.0 (Statacorp, TX).

**Results**

**Patient Characteristics**

Across the 1431 participants with vitamin D levels and a 2D transthoracic echocardiogram, the mean age was 60.1±10.5 years; 53% were men and 39% were African American (Table 1). The median eGFR was 46.4 (interquartile range [IQR], 34.6, 58.7) mL/min per 1.73 m^2. Eighty-four percent of the cohort had hypertension. Median 25(OH)D levels were 26.9 (IQR, 15.8, 37.1); 1,25(OH)D levels were 26.9 (IQR, 18.2, 36.9) pg/mL; PTH levels were 61 (IQR, 42, 93.5) pg/mL; and FGF23 levels were 123.5 (IQR, 83.8, 194.4) RU/mL, with moderate correlations among markers (Figure I and Table I in the online-only Data Supplement). As expected, low levels of the biomarker were associated with more advanced renal dysfunction, as measured by eGFR (*P*<0.001). In unadjusted models, each doubling in 1,25(OH)D was associated with a 6.5% lower LV mass (95% CI, −7.9, −5.0; *P*=0.001). Again, in adjusted models, including age, sex, African American race, BMI, eGFR, diabetes mellitus, tobacco use, ethanol use, and atrial fibrillation, this effect was attenuated, with a 1.4% lower LV mass with each doubling of 1,25(OH)D (95% CI, 0.10, −2.9; *P*=0.067). Consistent with our findings above, there was also a significant interaction between 1,25(OH)D and FGF23 on LV mass (interaction *P*=0.003). In participants with FGF23 levels greater than the median, each doubling of 1,25(OH)D was associated with a 2.6% lower LV mass (95% CI, −4.6, −0.5%; Table 3). Again, this effect differed in participants with low FGF23 levels (0.5%; 95% CI, −1.8, 2.8%). These findings suggest that the effects of 1,25(OH)D on LV mass are more evident in the setting of high FGF23 levels.

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There was no significant effect modification by PTH on the association between 25(OH)D or 1,25(OH)D and LV mass, although PTH was independently associated with LV mass in these adjusted models. There was a 1.8% (95% CI, 0.22, 3.4; *P*=0.026) higher LV mass with each doubling of PTH when considering 25(OH)D and FGF23, and a 2.2% (95% CI, 0.65, 3.7%; *P*=0.005) higher LV mass when considering 1,25(OH)D and FGF23. There was no significant effect modification by race, eGFR, or angiotensin-converting enzyme-inhibitor or angiotensin receptor blocker therapy. Consideration for potential confounders, including phosphate, albuminuria, cholesterol, cardiac disease history, systolic BP, season of blood draw, use of vitamin D supplements, baseline aldosterone levels, and hemoglobin, did not have any significant effect on our findings (data not shown).

**Associations Among Vitamin D, FGF23, PTH, and LV Mass**

25(OH)D levels were significantly associated with LV mass in unadjusted models, where each doubling in 25(OH)D level was associated with a 7.4% (95% CI, −5.9, −8.8; *P*<0.001) lower LV mass. After adjusting for multiple potential confounders, including age, sex, African American race, BMI, eGFR, diabetes mellitus, tobacco use, ethanol use, and atrial fibrillation, this effect remained significant (−1.6%; 95% CI, −0.1, −3.1; *P*=0.032). Furthermore, consideration of both PTH and FGF23 in these models revealed a significant interaction between FGF23 and 25(OH)D on LV mass (interaction *P*=0.016), independent of PTH levels. In participants with FGF23 levels greater than the median, each doubling of 25(OH)D was associated with a 2.5% lower LV mass (95% CI, −4.8, −0.2; Table 3). However, the effect of 25(OH)D on LV mass in the participants with FGF23 levels less than the median was significantly less pronounced (0.4%; 95% CI, −1.9, 2.7). These findings suggest that the effects of 25(OH)D on LV mass are more evident in the setting of high FGF23 levels.

**Associations Between Vitamin D Measures and LV Volumes and Ejection Fraction**

Given our findings above, subsequent analyses were performed in the context of a potential interaction between 25(OH)D and 1,25(OH)D and FGF23. In models adjusted for age, sex, African American race, BMI, eGFR, atrial fibrillation, and PTH, the relationships between 25(OH)D and LV EDV and ESV differed according to FGF23 (interaction *P*<0.02 and *P*<0.021,
Although the association between 25(OH)D and LV volumes was not statistically significant within each FGF23 stratum (Table 4), with each doubling of 25(OH)D, lower LV volumes were observed with FGF23 levels greater than the median and higher LV volumes were observed with FGF23 levels less than the median. Furthermore, 25(OH)D deficiency potentiated the adverse cardiac remodeling observed with increased FGF23 levels. As shown in Table 5, in participants with 25(OH)D deficiency, each doubling of FGF23 was associated with higher LV EDV compared with those with sufficient 25(OH)D levels (3.6% [95% CI, 1.4, 5.8] versus 2.0% [95% CI, 0.1, 3.8]). Similarly, in participants with 25(OH)D deficiency, each doubling of FGF23 was associated with higher LV ESV compared with those with sufficient 25(OH)D levels (5.8% [95% CI, 2.7, 9.0] versus 2.8% [95% CI, 0.1, 5.6]).

Our findings with 1,25(OH)2D were consistent with a significant interaction observed between 1,25(OH)2D and LV EDV and ESV (P=0.004 and P=0.001, respectively). Again, there were significant differences in the direction of the relationship between 1,25(OH)2D and volumes according to FGF23 levels (Table 4). Furthermore, the effects of FGF23 on LV ESV were

<table>
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<th>Parameter</th>
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<th>Women (N=670)</th>
</tr>
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<tbody>
<tr>
<td>Indexed LV mass, g/m2</td>
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<td>49.1±13.9</td>
</tr>
<tr>
<td>LWH</td>
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<td>302 (40)</td>
<td>287 (42)</td>
</tr>
<tr>
<td>Indexed end-diastolic LV volume, mL/m2</td>
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<td>34.2±8.4</td>
<td>31.6±8.2</td>
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<tr>
<td>Indexed end-systolic LV volume, mL/m2</td>
<td>15.2±6.8</td>
<td>16.2±7.5</td>
<td>14.1±5.7</td>
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<tr>
<td>Ejection fraction, %</td>
<td>54.9±8.1</td>
<td>53.8±8.6</td>
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</tr>
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</table>

Mean±SD or no. (%). LVH indicates left ventricular hypertrophy.

### Table 2. Echocardiographic Parameters of Cardiac Remodeling

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Mean±SD or no. (%). LVH indicates left ventricular hypertrophy.
more pronounced in the setting of 1,25(OH)₂D levels below the median when compared with above the median (5.4% [95% CI, 2.4, 8.5] versus 2.9% [0.2, 5.7]; Table 5).

Furthermore, there was no significant effect modification by PTH on the association between 25(OH)D or 1,25(OH)₂D and LV volumes, although there was an independent association between PTH and EDV (1.9%; 95% CI, 0.28, 3.5; \( P=0.021 \)) with each doubling of PTH. The percentage difference in LV mass (95% CI) associated with a doubling in vitamin D (either 25(OH)D or 1,25(OH)₂D) or FGF was estimated by \((2^{\beta_1}−1)×100\), where \( \beta_1 \) is the regression coefficient for (natural log) vitamin D or (natural log) FGF23. The 95% CI were estimated by \((2^{\text{Lower}−1})×100\) to \((2^{\text{Upper}−1})×100\), where Lower and Upper were the lower and upper values of the 95% CI for \( \beta_1 \), respectively. 1,25(OH)₂ indicates 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; LV, left ventricular; and PTH, parathyroid hormone.

In our cross-sectional analyses of 1431 patients with chronic renal insufficiency, we identified a significant interaction 25(OH)D and 1,25(OH)₂D and FGF23 on LV mass and volumes. Not only were the effects of 25(OH)D deficiency on increased LV mass more pronounced in the setting of elevated FGF23 levels but also 25(OH)D deficiency potentiated the risk of increased cardiac growth (LV mass) and cavity dilatation (LV EDV and ESV) with elevated FGF23 levels. Similarly, the association between 1,25(OH)₂D and LV mass was also more pronounced in the setting of elevated FGF23 levels, and 1,25(OH)₂D deficiency potentiated the risk of increased cardiac dilatation with elevated FGF23 levels. These effects were independent of PTH, suggesting that there are important effects of vitamin D on cardiac growth and hypertrophy even after consideration of the secondary hyperparathyroidism that occurs with vitamin D deficiency.

Table 3. Association Between Vitamin D Levels and LV Mass*  

<table>
<thead>
<tr>
<th>Marker</th>
<th>Percent Difference in LV Mass (95% CI)</th>
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<tr>
<td>Doubling of 25(OH)D</td>
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</tr>
<tr>
<td>FGF≥123.5 RU/mL</td>
<td>−2.5 (−4.8, −0.2)</td>
</tr>
<tr>
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<tr>
<td>25(OH)D≥20 ng/mL</td>
<td>1.6 (−0.2, 3.5)</td>
</tr>
<tr>
<td>25(OH)D&lt;20 ng/mL</td>
<td>3.4 (1.2, 5.6)</td>
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<tr>
<td>1,25(OH)D≥27.1 pg/mL</td>
<td>3.4 (1.5, 5.3)</td>
</tr>
<tr>
<td>1,25(OH)D&lt;27.1 pg/mL</td>
<td>1.9 (−0.1, 3.9)</td>
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*The regression models for log-transformed indexed LV mass include log-transformed vitamin D (either 25(OH)D or 1,25(OH)₂D) or log-transformed FGF23. In addition, the models include age, sex, African American race, BMI, eGFR, diabetes mellitus, tobacco use, ethanol use, atrial fibrillation, and natural log of PTH. The percentage difference in LV mass (with 95% CI) associated with a doubling in vitamin D (either 25(OH)D or 1,25(OH)₂D) or FGF was estimated by \((2^{\beta_1}−1)×100\), where \( \beta_1 \) is the regression coefficient for (natural log) vitamin D or (natural log) FGF23. The 95% CI were estimated by \((2^{\text{Lower}−1})×100\) to \((2^{\text{Upper}−1})×100\), where Lower and Upper were the lower and upper values of the 95% CI for \( \beta_1 \), respectively. 1,25(OH)₂ indicates 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; LV, left ventricular; and PTH, parathyroid hormone.

Discussion

CKD results in significant disturbances in bone and mineral metabolism. Vitamin D deficiency, secondary hyperparathyroidism, and marked elevations in FGF23 concentration are highly prevalent and are believed to contribute directly to cardiac hypertrophy and adverse cardiac remodeling. However, the interactions between these measures are poorly defined.

In our cross-sectional analyses of 1431 patients with chronic...
Doubling of 25(OH)D
Stratified by FGF23
FGF≥123.5 RU/mL -1.0 (−3.3, 1.4) -2.3 (−5.6, 1.2)
FGF<123.5 RU/mL 1.4 (−0.9, 3.8) 2.3 (−1, 5.6)

Doubling of 1,25(OH)2D
Stratified by FGF23
FGF≥123.5 RU/mL -1.2 (−3.3, 0.9) -1.9 (−4.9, 1.2)
FGF<123.5 RU/mL 1.3 (−1.3, 5.5) 2.7 (−0.5, 6.0)

*The regression models for log-transformed LV EDV or ESV include log-transformed vitamin D (either 25(OH)D or 1,25(OH)2D). In addition, the models include age, sex, African American race, BMI, eGFR, atrial fibrillation, and natural log of PTH. The percentage differences in LV EDV or ESV (with 95% CI) associated with a doubling in 25(OH)D are estimated as in Table 3. 1,25(OH)2D indicates 1,25-dihydroxyvitamin D; 25(OH)2D, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; EDV, end-diastolic volume; eGFR, estimated glomerular filtration rate; ESV, end-systolic volume; FGF23, fibroblast growth factor 23; LV, left ventricular; and PTH, parathyroid hormone.

Vascular smooth muscle cells or calcineurin activity.26,27 Others have hypothesized that secondary hyperparathyroidism may mediate the association between 25(OH)D and hypertrophy. PTH increases calcium levels and conversion of 25(OH)D to 1,25(OH)2D but has also been shown in observational studies to be associated with increased BP and is believed to have effects on vascular smooth muscle cells.12,26,27 PTH did have an independent association with LV mass and EDV in our adjusted models, corroborating the hypothesis that PTH may have some cardiac effects as well. However, the relationships we observed of 25(OH)D and FGF23 on cardiac remodeling were independent of PTH, suggesting that these 25(OH)D/FGF23 effects may occur through additional mechanisms.

FGF23 is associated with cardiac hypertrophy in human and animal studies.13 Klotho-deficient mice also developed significant LVH, and FGF23 administration results in pathological hypertrophy. Our findings provide additional insight into the complex interplay within the 25(OH)D, 1,25(OH)2D, and FGF23 axes by examining the interactions between these hormones. We found that vitamin D deficiency or FGF23 excess intensifies the adverse cardiac remodeling effects observed with either factor. These findings have important implications in determining which participants might derive the maximum benefit from pharmacological therapy to either modify vitamin D deficiency or FGF23 excess, and suggest that consideration of both metabolites is critical in establishing the effects of these measures on LV growth and remodeling.

Limitations of the study include the possibility for unmeasured confounding, although our models were comprehensive and included multiple potential confounders. Although we adjusted for BMI, we cannot completely exclude the possibility that unmeasured confounding between measures of adiposity, vitamin D, and LV mass contributed to the observed association between low vitamin D and increased LV mass. Furthermore, given the observational nature of our study, we cannot determine if adiposity potentially lies in the causal pathway between the relationship between vitamin D and LV mass. Furthermore, our FGF23 levels were obtained from a...
baseline blood sample, which was approximately 1 year before the assessment of all other variables. Our study design was cross-sectional in nature, limiting the causal inferences of our findings, which can be determined more definitively in longitudinal or in intervention studies. Nevertheless, this is the first study to demonstrate a significant interaction between 25(OH)D and 1,25(OH)D and FGF23 in humans and provide potential insight into future clinical trial design.

In summary, our findings demonstrate that in a large CKD cohort, 25(OH)D and 1,25(OH)D deficiency are independently associated with increased LV mass. There was a significant interaction by FGF23 on these relationships, whereby patients with elevated FGF23 levels had greater effects on LV mass and adverse cardiac remodeling. Similarly, deficiency in vitamin D potentiated the risk of adverse cardiac remodeling observed with elevated FGF23. These findings have important therapeutic implications in determining the effects of vitamin D repletion or FGF23 antagonists on cardiac remodeling.

Appendix

CRIC Study Investigators include: Lawrence J. Appel, MD, MPH; Harold I. Feldman, MD, MSCE; Alan S. Go, MD; Jiang He, MD, PhD; John W. Kusek, PhD; James P. Lash, MD; Akinlolu Ojo, MD, PhD; Mahboob Rahman, MD; Raymond R. Townsend, MD.

Disclosures

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References

22. Bloumen DA, Kromal RA, Lima JA, Liu K, Olson J, Burke GL, Folsom AR. The relationship of left ventricular mass and geometry
There is growing evidence to support an important role for vitamin D and related hormones, parathyroid hormone and fibroblast growth factor 23 (FGF23), on cardiac remodeling in chronic kidney disease. In 1431 participants from the Chronic Renal Insufficiency Cohort study, we measured 25(OH)D, 1,25(OH)_2D, FGF23, and PTH, and performed quantitative echocardiography measures of cardiac remodeling. Using linear regression methods, we determined significant negative interactions between 25(OH)D and FGF23 on cardiac size and remodeling, as measured by left ventricular mass, and end-diastolic and end-systolic volumes. Increased LV mass and cavity dilatation were observed with low 25(OH)D and high FGF23 levels. In other words, the effects of 25(OH)D deficiency on increased LV mass more pronounced in the setting of elevated FGF23 levels, and 25(OH)D deficiency potentiated the risk of increased cardiac growth and cavity dilatation with elevated FGF23 levels. Our findings suggest that consideration of both hormones is crucial to understanding the role of either in cardiac remodeling, and may have important therapeutic implications.
FGF23 Modifies the Relationship Between Vitamin D and Cardiac Remodeling
Bonnie Ky, Justine Shults, Martin G. Keane, Martin St. John Sutton, Myles Wolf, Harold I. Feldman, Peter P. Reese, Cheryl A. Anderson, Raymond R. Townsend, Rajat Deo, Joan Lo, Crystal Gadegbeku, Dean Carlow, Michael J. Sulik and Mary B. Leonard
and the CRIC Study Investigators*

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Supplemental Material

**Supplementary Figure 1A-D.** Distribution of Log Transformed Markers $25(OH)D$ (A), $1,25(OH)_2D$ (B), FGF23 (C), and PTH (D) Across the 1,431 Participants in CRIC.
Supplementary Table 1. Correlation Coefficients Across Vitamin D and Related Metabolites*

<table>
<thead>
<tr>
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<th>1,25(OH)₂D</th>
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<th>FGF23</th>
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*all p<0.001