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Mineral Metabolism and the Right Ventricle: The Multi-Ethnic Study of Atherosclerosis (MESA)

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To the Editor:

CKD is associated with cardiovascular disease including myocardial infarction, heart failure, and cardiovascular mortality. Altered mineral metabolism, often seen in CKD, may contribute to cardiovascular disease by promoting adverse cardiac remodeling. Specifically, excess PTH and FGF-23 and insufficient 1,25-dihydroxyvitamin D have direct effects on left ventricle (LV)¹⁻³ growth in experimental models.

Right heart failure also contributes to morbidity and mortality across a broad range of cardiopulmonary diseases. Increased right ventricle (RV) mass has been associated with incident heart failure and cardiovascular mortality⁴. Compared to the LV, the RV has a distinct geometry, fiber orientation, embryologic origin, and is upstream of the low-pressure pulmonary circulation. As a result, lessons learned in the LV cannot be directly translated to the RV. The impact of disturbed mineral metabolism on the RV is unknown.

We hypothesized that elevated serum concentrations of PTH and FGF-23 and lower serum concentrations of 25(OH)D are associated with increased RV mass and volumes and lower RV systolic function in MESA, a longitudinal cohort study of risk factors for subclinical

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Contributions: Research idea and study design: JSM, PJL, SMK, IHdB; data acquisition: JAL, DSS, BK, SMK, IHdB; data analysis/interpretation: PJL, JSM, NB, RD, JAL, DSS, BK, SMK, IHdB; statistical analysis: PJL; supervision or mentorship: SMK, IHdB. 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. SMK and IHdB take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

atherosclerosis⁵. Ancillary studies have measured serum biomarkers of mineral metabolism (PTH, FGF-23, 25(OH)D, phosphorus, and calcium) and RV morphology (mass, end-diastolic volume (EDV), and ejection fraction (EF)) by cardiac magnetic resonance imaging at the baseline visit (details in **Item S1**). For this study, we examined 3777 of 6814 MESA participants with measurements of mineral metabolism biomarkers and RV dimensions. Cross-sectional associations of mineral metabolism biomarkers with RV measures were tested using multivariable linear regression.

Study participants were racially and ethnically diverse with a normal eGFR (Table 1). Compared to those excluded, included participants had a lower prevalence of diabetes mellitus and hypertension and lower UACR and BMI (**Table 1**).

PTH, FGF-23, calcium, and phosphorus were not associated with RV mass, RVEF, or RVEDV (**Table 2, Table S1**). Lower 25(OH)D was associated with a slightly greater RV mass in unadjusted, but not adjusted, analyses. Unadjusted associations are likely limited given confounding by body size. In adjusted analyses, lower 25(OH)D was associated with higher RVEF and lower RVEDV. Limited models adjusting for body size alone were similar to fully adjusted models (Table S1).

The lack of association between mineral metabolism biomarkers and RV mass in our large, community-based cohort was surprising and contrary to our hypothesis. These results contrast with published studies, including MESA data, suggesting that disturbed mineral metabolism may promote LV hypertrophy^{1-3, 6}.

Given our large cohort and precise RV mass measurements, insufficient power and misclassification seem unlikely to explain our null results. The ranges of PTH and FGF-23 were limited in this cohort with predominantly normal eGFR, however, and results might differ with more advanced kidney disease. Our null associations may suggest differential relationships of abnormal mineral metabolism on the LV relative to the RV.

The ventricles are distinct⁷: the LV originates from the primary heart field whereas the RV arises from the anterior heart field. The LV is elliptical whereas the RV is triangular or crescentic. The LV is thicker and has more mass than the RV and as such, is better suited to handle pressure overload. The more compliant RV is better equipped to handle volume overload. Given their inherent differences and unique responses to physiologic insults, it is conceivable that mineral metabolism alterations affect each ventricle differently.

Unexpectedly, lower 25(OH)D concentrations were associated with lower RVEDV and higher RVEF. This observation is counterintuitive because higher RVEF is associated with better outcomes in heart failure⁸ and pulmonary arterial hypertension⁹, but low 25(OH)D is typically associated with poor outcomes. One potential explanation is that lower 25(OH)D concentrations could lead to decreased RV compliance, such as that seen with mild fibrosis or diastolic dysfunction. This would be expected to result in a decreased RVEDV,¹⁰ as was observed. In this relatively healthy population, compensation to maintain cardiac output would require increases in heart rate or RVEF. Unfortunately methods to identify fibrosis and diastolic dysfunction in the RV are not widely agreed on and these data were not available in MESA.

Our study strengths include large size, a community-based multiethnic cohort free of baseline cardiovascular disease (reducing the likelihood of reverse causality), a comprehensive assessment of mineral metabolism markers, and precise RV measurements. Limitations include cross-sectional design; limited ranges of eGFR, PTH, and FGF-23; and lack of clinical outcomes.

In conclusion, unlike associations established for the LV, mineral metabolism biomarkers were not associated with RV mass in a diverse, community-based population. Associations of 25(OH)D with RVEDV and RVEF were small, but hypothesis generating.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of the participants in MESA

Parameter	Study Sample (n=3777)	Excluded (n=3037)
Age (y)	61.4 ± 10.1	63.1 ± 10.3
Female	53.1%	52.5%
Race		
White	40.0%	36.6%
Chinese	13.1%	10.2%
African-American	25.1%	31.1%
Hispanic	21.8%	22.2%
Height (cm)	166.3 ± 9.9	166.4 ± 10.1
Weight (kg)	77.2 ± 16.2	80.5 ± 18.5
BMI (kg/m ²)	27.8 ± 5.0	29.0 ± 6.0
Educational attainment		
No high school diploma	15.9%	20.8%
High school degree	18.1%	18.3%
Some college	16.0%	16.7%
Bachelor's Degree	18.4%	15.8%
Higher than bachelor's degree	19.0%	16.7%
Cigarette smoking status		
Never	52.9%	47.1%
Former	34.6%	39.2%
Current	12.5%	13.8%
Hypertension	42.3%	48.4%
Systolic blood pressure (mmHg)	125.3 ± 21.0	128.3 ± 22.0
Diabetes mellitus	12.1%	15.4%
UACR (mg/g)	21.9 ± 123.8	33.4 ± 214.9
eGFR (mL/min/1.73m ²)	86.0 ± 17.0	83.2 ± 18.4
PTH (pg/mL)	44.2 ± 21.3	45.3 ± 22.4
25(OH)D (ng/mL)	26.2 ± 11.0	25.0 ± 11.5
FGF-23 (ng/mL)	40.0 ± 18.1	40.7 ± 18.8
Calcium (mg/mL)	9.7 ± 0.4	9.6 ± 0.4
Phosphate (mg/mL)	3.7 ± 0.5	3.7 ± 0.5
RV Mass (g)	21.0 ± 4.4	21.5 ± 4.7*
RVEDV (mL)	124.1 ± 30.8	124.8 ± 31.1*
RVEF(%)	70.6 ± 6.4	68.7 ± 6.8*
LV Mass (g)	145.3 ± 39.2	145.2 ± 40.5*
LVEDV (mL)	126.6 ± 31.5	125.6 ± 31.7*
LVEF (%)	69.1 ± 7.3	68.8 ± 7.8*

Continuous variables given as mean $\pm$ SD. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone; UACR, urinary albumin-creatinine ratio;

Mineral metabolism biomarker reference values: PTH <65 pg/mL, 25(OH)D >30 ng/mL, Calcium 8.5-10.3 mg/mL, Phosphate 2.5-4.5 mg/mL

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Table 2

Associations of PTH, 25(OH)D, FGF-23, and RV structure and function.

	RV Mass (g)		RVEF(%)		RVEDV (mL)	
	Unadjusted mean $\pm$ SD	Adjusted difference (95% CI)	Unadjusted mean $\pm$ SD	Adjusted difference (95% CI)	Unadjusted mean $\pm$ SD	Adjusted difference (95% CI)
PTH						
<65 pg/mL	21.0 $\pm$ 4.4	Referent	70.6 $\pm$ 6.4	Referent	123.9 $\pm$ 30.9	Referent
$\geq$ 65 pg/mL	21.3 $\pm$ 4.5	0.3 (−0.1, 0.6)	70.9 $\pm$ 6.8	0.1 (−0.5, 0.8)	125.7 $\pm$ 30.4	1.1 (−1.1, 3.3)
P		0.1		0.7		0.3
25(OH)D						
>30ng/mL	20.6 $\pm$ 4.3	Referent	70.6 $\pm$ 6.5	Referent	121.9 $\pm$ 31.3	Referent
20-30ng/mL	21.0 $\pm$ 4.5	−0.1 (−0.4, 0.1)	70.6 $\pm$ 6.2	0.5(0.0, 1.0)	123.5 $\pm$ 30.8	−2.1 (−3.7, −0.5)
<20ng/mL	21.5 $\pm$ 4.4	−0.1 (−0.4, 0.2)	70.7 $\pm$ 6.6	0.9(0.3, 1.4)	127.4 $\pm$ 30.1	−1.6 (−3.4, 0.2)
P for trend		0.7		0.006*		0.04*
FGF-23						
<30.5 ng/mL	20.4 $\pm$ 4.2	Referent	71.1 $\pm$ 6.3	Referent	120.3 $\pm$ 29.3	Referent
30.5-37.7 ng/mL	21.1 $\pm$ 4.3	0.3 (0.0, 0.6)	70.5 $\pm$ 6.4	−0.4(−0.9, 0.2)	124.9 $\pm$ 30.9	2.2 (0.3, 4.0)
37.7-46.4 ng/mL	21.2 $\pm$ 4.3	0.1 (−0.2, 0.4)	70.5 $\pm$ 6.4	−0.2(−0.7, 0.4)	125.4 $\pm$ 30.2	0.2 (−1.7, 2.1)
>46.4 ng/mL	21.4 $\pm$ 4.8	0.3 (0.0, 0.6)	70.4 $\pm$ 6.5	−0.5(−1.0, 0.1)	126.1 $\pm$ 32.7	1.2 (−0.7, 3.2)
P for trend		0.08		0.4		0.08

Differences are adjusted for age, sex, race/ethnicity, study site, height, weight, education, income, smoking, hypertension, diabetes mellitus, low density lipoprotein-cholesterol, triglycerides, fasting glucose, eGFR, and UACR using multivariable linear regression.