The Authors Reply: We thank Milovanova *et al.*[1] for their comments regarding our manuscript reporting the association of fibroblast growth factor 23 (FGF-23) with left ventricular (LV) diastolic dysfunction in hemodialysis patients.[2] Consistent with our findings, Milovanova *et al*. also demonstrated a correlation between FGF-23 levels and LV diastolic function in 51 patients with advanced chronic kidney disease (CKD), of whom 26 were treated with hemodialysis and 78% had an LV ejection fraction >50%.[1] However, they also measured Klotho, and observed that serum Klotho levels correlated with LV diastolic function as well. Whereas the association between higher FGF-23 levels and more severe LV diastolic dysfunction did not persist in multivariate analysis including Klotho as a covariate, the association between lower Klotho levels and more severe LV diastolic dysfunction persisted, despite adjustment for FGF-23.

A number of limitations within the available report prevent complete assessment of the authors' findings. First, and importantly, details about assay characteristics for Klotho and FGF-23 are missing. Prior studies using immune-based assays have shown widely disparate absolute values of soluble Klotho, along with inconsistencies in the directions of association with key variables including estimated glomerular filtration rate and age.[3,4] This has raised considerable concerns about the quality of commercially available Klotho assays.[S1,S2] Second, although echocardiography is the primary imaging modality used for evaluation of LV diastolic dysfunction, several classifications exist, of which details were not reported.[S3] Third, because specific details of the regression models were not described, it is unclear to what degree the FGF-23—diastolic function association was attenuated. In studies with small sample sizes, it is helpful to understand changes in the parameter estimates for each of the nested models when evaluating the degree of attenuation, rather than simply the statistical significance of parent versus nested models.

Existing studies suggest that FGF-23 mediates effects on cardiac myocytes through pathways that do not require Klotho.[S4] Lower circulating Klotho levels may also adversely affect the heart independently of FGF-23.[S5] Indeed, Klotho—both membrane-bound and soluble—is an important factor, and is key to fully understanding CKD-associated cardiac disease. Unfortunately, the reliability of available commercial Klotho assays and the standardization of measurement techniques remain variable. Taking into consideration these limitations, statistical adjustments showing a dampened effect between FGF-23 and diastolic dysfunction may not necessarily imply that observed relationships are biologically driven by FGF-23 and Klotho. This is particularly relevant, when each biomarker and diastolic function was measured cross-sectionally. To properly assess the full implications of the complex relationships among Klotho, FGF-23, and LV diastolic function, future studies need to carefully consider detailing assay characteristics, other relevant mineral metabolism markers that may affect outcomes (such as phosphate, parathyroid hormone, and calcium), and specific classification characteristics used for grading diastolic function.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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