The Effects of Intensive Blood Pressure Lowering on Markers of Mineral Metabolism in Persons with CKD in SPRINT

Charles Ginsberg,1,2 Ronit Katz,3 Michel B. Chonchol,4 Alexander L. Bullen,1,2 Kalani L. Raphael,5 William R. Zhang,6,7 Walter T. Ambrosius,8 Jeffrey T. Bates,9 Javier A. Neyra,10 Anthony A. Killeen,11 Henry Punzi,12 Michael G. Shlipak,8,13 and Joachim H. Ix1,2

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Research Letter

Serum concentrations of fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) are elevated in patients with CKD, and higher concentrations are well established as risk factors for cardiovascular disease and death (1). In the Systolic Blood Pressure Intervention Trial (SPRINT), intensive systolic BP lowering led to lower rates of cardiovascular events and mortality despite a more rapid decline in eGFR (2). Given that FGF23 and PTH would be expected to increase in the setting of declining eGFR, the effects of intensive systolic BP control on these key potential intermediates are of considerable interest.

The SPRINT, described in detail elsewhere (2,3), was a randomized, controlled trial among nondiabetic persons with hypertension evaluating the effects of intensive systolic BP lowering (<120 mm Hg) versus standard systolic BP target (<140 mm Hg). Of the 9361 participants enrolled in the SPRINT, 1000 participants with an eGFR<60 ml/min per 1.73 m² were randomly chosen to have repeated serum measurements of intact FGF23 (Kainos), intact PTH, calcium, phosphate, and urine creatinine and phosphate (4). Using these data, we calculated fractional excretion of phosphate (FePhos) and fractional excretion of calcium. We evaluated the changes in each parameter from baseline to year 1 stratified by intervention status. We used linear mixed models to evaluate the effect of randomization to the intensive BP lowering arm on longitudinal changes in serum FGF23, PTH, calcium, phosphate, FePhos, and fractional excretion of calcium.

Of the 1000 participants with CKD randomly sampled for this study, 987 had specimens available at year 1. Baseline characteristics stratified by intervention arm are reported elsewhere (5). The mean age was 72±9 years old, 42% were women, and the mean eGFR was 46±10 ml/min per 1.73 m². Baseline intact FGF23 concentrations were 65 and 66 pg/ml in the standard and intensive arms, respectively. The mean eGFR changes were +1.58 and −2.12 ml/min per 1.73 m² in the standard and intensive arms, respectively. Compared with participants in the standard arm, participants in the intensive arm experienced an 11.5% (95% confidence interval, 6.0 to 17.0) increase in FGF23 over the year (Table 1). This relative difference in FGF23 was unchanged by adjustment for concurrent changes in eGFR and albuminuria. There were no relative differences in serum PTH, calcium, or phosphate across treatment arms. In parallel with the increase in FGF23 in the intensive arm, FePhos rose by 4.2% in the intensive arm relative to the standard arm, although this association was not statistically significant (P=0.15).

In this analysis of randomized, controlled trial participants with hypertension and CKD, we demonstrate that randomization to the intensive BP arm resulted in a relative increase in FGF23 over 1 year and was accompanied with a nonsignificant increase in FePhos. Moreover, the change in FGF23 did not seem to be explained by the observed concurrent decrease in eGFR.

The clinical implications of these findings are uncertain. Although longitudinal increases in FGF23 levels have been associated with greater cardiovascular risk in patients with CKD (6), the intensive arm of the SPRINT experienced lower cardiovascular events and mortality risk despite the concurrent rise in FGF23 (2). Thus, mechanisms leading from intensive BP lowering to cardiovascular protection are likely via pathways distinct from FGF23.

A priori, we hypothesized that reductions in eGFR due to intensive BP lowering would lead to increases in FGF23 and PTH. However, we found that the increases in FGF23 persisted despite accounting for concurrent changes in eGFR, and PTH did not change. These findings suggest that mechanisms beyond changes in eGFR may be driving increases in FGF23. Responsible mechanisms and the examination of other markers of mineral metabolism (e.g., Klotho) require additional investigation. The observed rise in FePhos in the intensive arm suggests that the changes in FGF23 may be biologically meaningful.

This study has important limitations. Implicit in the evaluation of 1-year changes in FGF23, participants had to survive to year 1, and some participants had cardiovascular events prior to the year 1 measurement. It would be optimal to examine the association of changes in FGF23 with subsequent cardiovascular
risk. However, this inherent survival bias to year 1, the small sample size with repeated measurement, and the short-term follow-up after year 1 in the SPRINT preclude us from evaluating the clinical consequences of these increases in FGF23. We previously found that baseline FGF23 concentrations in the SPRINT had no independent associations with cardiovascular events or mortality after adjustment for eGFR (4). In addition, among SPRINT participants with CKD, randomization to the intensive arm was associated with a statistically significant reduction in mortality risk (2). Thus, although a longitudinal rise in FGF23 is of high interest and warrants future study, we do not believe that these findings should dissuade clinicians from pursuing aggressive systolic BP lowering in their patients with CKD.

In conclusion, among SPRINT participants with CKD, those randomized to the intensive BP arm experienced a 12% relative increase in serum FGF23 over 1 year compared with participants in the standard arm. Further investigation is needed to understand the clinical consequences of changes in FGF23 that occur during intensive BP lowering.

Acknowledgments

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Table 1. Effect of intensive BP therapy on markers of mineral metabolism

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Arm, % Change/yr (95% CI)</th>
<th>Standard Arm, % Change/yr (95% CI)</th>
<th>Difference between Arms, % Change/yr (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔIntact FGF23</td>
<td>−0.6 (−4.4 to 3.2)</td>
<td>−12.1 (−16.1 to −8.0)</td>
<td>11.5 (6.0 to 17.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>ΔIntact PTH</td>
<td>−4.6 (−7.7 to −1.4)</td>
<td>−3.0 (−6.1 to 0.1)</td>
<td>−1.6 (−6.1 to 2.9)</td>
<td>0.33</td>
</tr>
<tr>
<td>ΔPhosphate</td>
<td>1.19 (0.08 to 2.31)</td>
<td>−0.06 (−1.24 to 1.13)</td>
<td>1.25 (−0.38 to 2.88)</td>
<td>0.13</td>
</tr>
<tr>
<td>ΔCalcium</td>
<td>0.26 (−0.23 to 0.74)</td>
<td>0.13 (−0.39 to 0.65)</td>
<td>0.13 (−0.59 to 0.84)</td>
<td>0.73</td>
</tr>
<tr>
<td>ΔFractional excretion of phosphate</td>
<td>2.69 (−1.17 to 6.56)</td>
<td>−1.49 (−5.56 to 2.60)</td>
<td>4.18 (−1.45 to 9.80)</td>
<td>0.15</td>
</tr>
<tr>
<td>ΔFractional excretion of calcium</td>
<td>−13.46 (−21.17 to −5.78)</td>
<td>−7.83 (−15.89 to 0.32)</td>
<td>−5.63 (−16.85 to 5.56)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

95% CI, 95% confidence interval; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone.

aValues adjusted for baseline concentrations.

bStandard arm serves as reference.

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References

3. Wright JT Jr., Williamson JD, Snyder JK, Sink KM, Rocco MC, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL,


M.G.S. and J.H.I. contributed equally to this work.

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AFFILIATIONS

1Nephrology Section, Veterans Affairs San Diego Healthcare System, San Diego, California
2Division of Nephrology-Hypertension, University of California, San Diego, California
3Kidney Research Institute, University of Washington, Seattle, Washington
4Division of Renal Diseases and Hypertension, University of Anschutz Medical Center, Aurora, Colorado
5Division of Nephrology and Hypertension, University of Utah Health, Salt Lake City, Utah
6Kidney Health Research Collaborative, Veterans Affairs Medical Center, San Francisco, California
7Department of Dermatology, University of California, San Francisco, California
8Division of Public Health Sciences, Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, North Carolina
9Department of Medicine, Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Texas
10Division of Nephrology, Bone and Mineral Metabolism, Department of Internal Medicine, University of Kentucky, Lexington, Kentucky
11Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston, Massachusetts
12Punzi Medical Center, Carrollton, Texas
13Department of Medicine, University of California, San Francisco, California