Treatment of Serum Phosphate in Early CKD

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Denver Nephrology Research
Disclosure of Interests

- Amgen: Consultancy, research grant
- Keryx: Consultancy, honoraria
- Sanofi: No current relationships, past honoraria, research grant sponsored education grants
- Shire: No current relationship, past research grant
- JTT: Consultancy
Treatment of Phosphate in Early Chronic Kidney Disease

- **4.1.1.** In patients with CKD stages 3–5, we suggest *maintaining serum phosphorus in the normal range (2C)*

- **4.1.4.** In patients with CKD stages 3–5 (2D) and 5D (2B), *we suggest using phosphate-binding agents in the treatment of hyperphosphatemia. It is reasonable that the choice of phosphate binder takes into account CKD stage, presence of other components of CKD–MBD, concomitant therapies, and side-effect profile*

- **4.1.5.** In patients with CKD stages 3–5D and hyperphosphatemia, *we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia (1B)*

- In patients with CKD stages 3–5D and hyperphosphatemia, *we suggest restricting the dose of calcium-based phosphate binders in the presence of arterial calcification (2C)*

- **4.1.7.** In patients with CKD stages 3–5D, *we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (2D)*
Phosphate Homeostasis
Survival According to Phosphate Levels Relative to KDIGO Guidelines

Hazard Ratio
In Target: 1.8 (0.98, 3.8) \( p = 0.06 \)
Above Target: 2.7 (1.3, 5.7) \( p = 0.009 \)

Years Follow Up
Analysis adjusted for age, gender, proteinuria, diabetes, hemoglobin, systolic blood pressure, current smoking status, cardiovascular disease, eGFR, and vitamin D analog and phosphate binder use.

Serum Phosphate Modifies Risk of CKD Progression

I/II quartile: <3.45 mg/dl. III quartile: 3.45 to 4.00 mg/dl. IV quartile: >4.00 mg/dl.


N=331; p< .0025 after adjustment for GFR, proteinuria, ramipril, albumin, gender, systolic BP
Composite End Point of ESRD or Death According to Serum Phosphorous Levels

**Overall Likelihood**

**Hazard Ratio**

*Adjusted for age, case mix, hemoglobin, total calcium, uric acid and ACE inhibitors, vitamin D, and calcium salts use


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**Composite Endpoint Probability**

- Low Quartile
- Mid-low Quartile
- Mid-high Quartile
- High Quartile

**Hazard Ratio (HR)**

- Quartile 1
- Median
- Quartile 3

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**Time (Months)**

0 10 20 30 40

**Composite Endpoint Probability**

0.0 0.2 0.4 0.6 0.8 1.0

**Hazard Ratio**

0.0 0.6 1.0 1.6 2.7

95% CI

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**HR According to Serum Phosphorus Level**

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CKD-MBD Controversies Conference | October 25-27, 2013 | Madrid, Spain
Association Between Hyperphosphatemia and the Composite Outcome (Death or Progression to ESRD) In the Study Cohort

Overall (n=1716)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age-Adjusted</th>
<th>Case Mix Model*</th>
<th>Cox Full Model†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>P&lt;3.3 mg/dl</td>
<td>0.64</td>
<td>0.42 to 0.96</td>
<td>0.03</td>
</tr>
<tr>
<td>P≥3.3 and &lt;3.8</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>P≥3.8 and &lt;4.3</td>
<td>1.29</td>
<td>0.91 to 1.81</td>
<td>0.14</td>
</tr>
<tr>
<td>P≥4.3</td>
<td>4.01</td>
<td>2.93 to 5.47</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Case mix: age + gender, eGFR, history of diabetes mellitus, history of hypertension, and history of COPD and CVD.
† Full model: age + case mix + hemoglobin, total calcium, uric acid and ACE inhibitors, vitamin D, and calcium salts use.
Prevalence of Coronary Artery Calcium (CAC) Score > 100 in CRIC Cohort

**Fibroblast Growth Factor 23**

- Quartile 1: Prevalence Ratio (95% CI) = 0.5
- Quartile 2: Prevalence Ratio (95% CI) = 1.0
- Quartile 3: Prevalence Ratio (95% CI) = 2.0
- Quartile 4: Prevalence Ratio (95% CI) = 3.0

*p*-trend = 0.62

**Serum Phosphate**

- Quartile 1: Prevalence Ratio (95% CI) = 0.5
- Quartile 2: Prevalence Ratio (95% CI) = 1.0
- Quartile 3: Prevalence Ratio (95% CI) = 2.0
- Quartile 4: Prevalence Ratio (95% CI) = 3.0

*p*-trend < 0.01

I models adjusted for age, sex, race, ethnicity, eGFR, uACR, CVD, diabetes, smoking, HTN, high cholesterol, BMI, PTH, Ca and center and either FGF23 or P

WHERE ARE WE?
PROGRESS

START

KDIGO

FINISH
Phosphate Absorption: Sodium Dependent, Sodium Independent

Binder

Phosphate transport inhibitor

Phosphate

Transporter

Enterocyte

Capillary

Phosphate Absorption: Sodium Dependent, Sodium Independent
NPT2B Expression in CKD with or without P Binders

Schiavi, JASN 2012

*p<0.05 vs adenine n=8-10/group
Niacin with or without Laropiprant: Differential Effects on Serum P and FGF23

Rao et al, Submitted NDT 2013
Yamamoto, Kidney Int, 2012, MESA study
MDRD Study A- 585 subjects with eGFR 25-55 ml/min with usual vs. low protein diet

Block, AJKD 2013
Change in Biochemical Markers

**Fibroblast Growth Factor 23**

**Serum Phosphate**

Combined Effects of Lanthanum carbonate (LC) and Dietary Intervention on Fibroblast Growth Factor 23 (FGF23)

**Change in Serum Phosphate**

**Change in FGF23**

**Changes in Serum Phosphate (S-Pi) Concentration**

![Graph showing changes in serum phosphate concentration over time with different groups (Monophosphate, Polyphosphate, Control) and supplemental administration times. The graph includes error bars and indicates significance with ANOVA, p=0.0001.

*Significantly different from control session
Effects of ‘Real’ Food +/- P Binder

**Phosphate**

- Baseline: 1113.9
- Normal P Diet: 723.2
- Low P Diet: 522.7
- High P Diet: 455.0
- CKD: 315.0

**PTH**

- Normal P Diet: 726.9
- Low P Diet: 726.9
- High P Diet: 726.9
Association with All-Cause Mortality by Serum P, Urine P:C and Urine FeP

**Serum Phosphorus**

- Q1: <3.0
- Q2: 3.0-3.2
- Q3: 3.3-3.5
- Q4: ≥3.6

**Urine Phosphorus-Creatinine Ratio**

- Q1: <0.33
- Q2: 0.33-0.42
- Q3: 0.43-0.54
- Q4: ≥0.55

**Urinary Fractional Excretion of Phosphorus**

- Q1: <10
- Q2: 10-13
- Q3: 14-17
- Q4: ≥18

*Reference. Associations given as hazard ratio (95% CI)

Study Design

Run-in Phase
- Recruited: n=120
- Sevelamer 1600 mg tds

Randomization
- n=109

Blinded Treatment Phase
- Treatment Group: Sevelamer 1600 mg tds
  - n=55
  - Completed Follow-up: n=50
  - Intent-to-Treat Analysis: n=54

Placebo Group: Placebo tds
  - n=54
  - Completed Follow-up: n=47
  - Intent-to-Treat Analysis: n=50

Final Investigations

Initial Investigations
- Screened: n=1297
- Recruited: n=120

Week 0
- Initial Investigations

Week 4
- Sevelamer 1600 mg tds

Week 40
- Completed


CKD-MBD Controversies Conference | October 25-27, 2013 | Madrid, Spain
## Treatment Effects

<table>
<thead>
<tr>
<th>Biochemical</th>
<th>Placebo (n=50)</th>
<th>Sevelamer (n=54)</th>
<th>Mean Difference in Change Between Groups</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 40</td>
<td>Week 0</td>
<td>Week 40</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>49±13</td>
<td>50±14</td>
<td>49±13</td>
<td>48±14</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>26.4±2.8</td>
<td>27.2±3.4</td>
<td>27.0±2.7</td>
<td>27.2±6.2</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>181±42</td>
<td>170±46</td>
<td>193±50</td>
<td>166±54</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>105±36</td>
<td>100±42</td>
<td>106±35</td>
<td>92±39</td>
</tr>
<tr>
<td>Phosphate (mg/dl)</td>
<td>3.25±0.53</td>
<td>3.31±0.53</td>
<td>3.16±0.50</td>
<td>3.16±0.71</td>
</tr>
<tr>
<td>Corrected calcium (mg/dl)</td>
<td>8.80±0.40</td>
<td>8.76±0.32</td>
<td>8.88±0.36</td>
<td>8.84±0.32</td>
</tr>
<tr>
<td>PTH (pg/ml)*</td>
<td>54 (37–73)</td>
<td>51 (39–72)</td>
<td>52 (39–70)</td>
<td>52 (35–75)</td>
</tr>
<tr>
<td>FGF-23 (pg/ml)*</td>
<td>67.6 (51.1–87.7)</td>
<td>63.6 (52.0–83.6)</td>
<td>70.8 (52.5–83.0)</td>
<td>65.9 (49.2–90.7)</td>
</tr>
<tr>
<td>Klotho (pg/ml)</td>
<td>869±279</td>
<td>873±320</td>
<td>1001±500</td>
<td>980±533</td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D (pg/ml)</td>
<td>28.8±12.7</td>
<td>26.1±10.8</td>
<td>28.5±10.3</td>
<td>27.3±10.4</td>
</tr>
<tr>
<td>25-hydroxyvitamin D (ng/ml)</td>
<td>22.2±12.5</td>
<td>21.9±12.3</td>
<td>23.0±11.2</td>
<td>23.4±13.3</td>
</tr>
</tbody>
</table>

*Log-transformed before analysis.

Lanthanum Carbonate vs. Placebo in Stage 3 CKD

LaCO$_3$ vs. Placebo

<table>
<thead>
<tr>
<th>Urinary Phosphorus (mg/day)</th>
<th>Baseline</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1600</td>
<td>1400</td>
</tr>
<tr>
<td></td>
<td>1200</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td>800</td>
<td>800</td>
</tr>
<tr>
<td></td>
<td>600</td>
<td>600</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>

38 subjects- no dietary intervention. La 1000 mg TID

FGF23 Levels

LaCO$_3$

Plasma FGF23 (pg/ml)

Baseline | 12 Months

Placebo

Plasma FGF23 (pg/ml)

Baseline | 12 Months

Effect of LaCO$_3$ on PWV

## Calcium Acetate vs. Sevelamer in CKD

<table>
<thead>
<tr>
<th></th>
<th>Sevelamer Baseline</th>
<th>Sevelamer 8 Wk</th>
<th>% Change (95% Cl)</th>
<th>Calcium Acetate Baseline</th>
<th>Calcium Acetate 8 Wk</th>
<th>% Change (95% Cl)</th>
<th>Diff Btw % Δ at 8 Wk (95% Cl)*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum phosphate (mg/dl)</strong></td>
<td>7.7</td>
<td>5.3</td>
<td>-31.1 (-34.9 to -27.1)</td>
<td>7.7</td>
<td>6.5</td>
<td>-14.9 (-19.1 to -10.9)</td>
<td>-16.2 (-15.8 to -16.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>iPTH (pg/mL)</strong></td>
<td>159.4</td>
<td>166.1</td>
<td>4.5 (0.3 to 8.7)</td>
<td>145.9</td>
<td>161.5</td>
<td>11.7 (5.6 to 17.8)</td>
<td>-7.2 (-5.3 to -9.1)</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>FGF-23 (pg/mL)</strong></td>
<td>39.9</td>
<td>28.9</td>
<td>-27.1 (-33.2 to -8.8)</td>
<td>38.9</td>
<td>37.4</td>
<td>3.5 (-8.4 to 12.1)</td>
<td>-30.6 (-20.9 to -41.6)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>eGFR (mL/min/1.73 m²)</strong></td>
<td>23.8</td>
<td>22.4</td>
<td>-5.3 (-8.9 to -1.6)</td>
<td>21.9</td>
<td>20.7</td>
<td>-4.7 (-8.3 to -1.1)</td>
<td>-0.6 (-0.7 to 0.6)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

N= 47 Sevelamer; 53 Calcium Acetate
† Statistical analysis comparing changes seen with sevelamer with those seen with calcium acetate.
PILOT study with primary goal to inform treatment effect for design of larger outcome based RCT
Does active treatment with P binders lower serum P over 9 months compared to placebo?
Does reduction of serum P OR treatment with P binders affect biochemical, vascular or skeletal outcomes?

VISIT SCHEDULE
Screen, Baseline, Week 2, Month 1, Month 2, Month 3, Month 6, Month 9

eGFR 20-45
Serum P (2 Values) >3.5 - ≤ 6.0

Follow Up 5 year RRT Death

3 Lanthanum Carbonate
2 Matching Placebo

3 Calcium Acetate
2 Matching Placebo

3 Sevelamer Carbonate
2 Matching Placebo

Does a cave treatment with P binders lower serum P over 9 months compared to placebo?
Does reduction of serum P OR treatment with P binders affect biochemical, vascular or skeletal outcomes?
Balance and kinetic study design

- Randomized placebo-controlled trial with cross-over in 7 patients with CKD stage 3/4

- Week 1 of each 3 week balance period – equilibration period

- Weeks 2 & 3 of each 3 week balance period – urine and fecal collections
Challenging the Concept of Phosphate ‘Load’

Phosphorus mg/d

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet P</td>
<td>1564</td>
<td>1564</td>
</tr>
<tr>
<td>Fecal P</td>
<td>765</td>
<td>881</td>
</tr>
<tr>
<td>Urine P</td>
<td>807</td>
<td>638</td>
</tr>
<tr>
<td>P Balance</td>
<td>N.S.</td>
<td>-19</td>
</tr>
</tbody>
</table>

Hill et al, 2012
Calcium Balance

**Diet Ca**
- Placebo: 957 mg/d
- Calcium: 2457 mg/d
  - p < 0.001

**Fecal Ca**
- Placebo: 884 mg/d
- Calcium: 2004 mg/d
  - *p < 0.001

**Urine Ca**
- Placebo: 57 mg/d
- Calcium: 53 mg/d
  - N.S.

**Ca Balance**
- Placebo: 21 mg/d
- Calcium: 392 mg/d
  - *p = 0.03
Calcium Absorption in CKD

Table 2. Participants’ laboratory results

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Baseline</th>
<th>Post-treatment</th>
<th>Change</th>
<th>P (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FxAbs (%)(^b)</td>
<td>12 (7–17)</td>
<td>12 (7–16)</td>
<td>0.01 (−0.05 to 0.03)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>14.2 (11.5–18.5)</td>
<td>49.3 (42.3–58.1)</td>
<td>32.0 (27.5–40.6)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.0 (8.5–9.5)</td>
<td>9.0 (8.5–9.2)</td>
<td>−0.0 (−0.3 to 0.1)</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.6 (3.4–3.8)</td>
<td>3.6 (3.4–3.9)</td>
<td>0.1 (−0.0 to 0.2)</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>Corrected calcium(^c)</td>
<td>9.3 (8.7–9.9)</td>
<td>9.2 (8.8–9.6)</td>
<td>−0.2 (−0.3 to 0.4)</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>5.9 (4.7–7.1)</td>
<td>5.8 (4.7–6.6)</td>
<td>−0.5 (−1.3 to 0.7)</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Parathyroid hormone (pg/ml)</td>
<td>325 (218–552)</td>
<td>376 (269–611)</td>
<td>42 (−127 to 218)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>1,25(OH)(_2)D (pg/ml)</td>
<td>15.1 (10.5–18.8)</td>
<td>20.5 (17.0–24.7)</td>
<td>5.6 (1.9–11.1)</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

Median (interquartile range).

\(^a\)P value for individual change from baseline to end of study (paired t test).

\(^b\)Calcium absorption fraction.

\(^c\)Corrected calcium=((0.8×(4.0−subject’s albumin))+subject’s serum calcium).
Effect of High Calcium Diet on FGF23

Event-Free Survival from the Composite End Point of All-Cause Mortality and Dialysis Inception Among Treated Patients

After adjustment for age, sex, diabetes, HTN, CrCL, baseline CAC there was a significant reduction HR .62 for composite (.40-.97) events.

<table>
<thead>
<tr>
<th></th>
<th>Sevelamer (n=107)</th>
<th>Calcium Carbonate (n=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>107</td>
<td>105</td>
</tr>
<tr>
<td>6</td>
<td>106</td>
<td>103</td>
</tr>
<tr>
<td>12</td>
<td>98</td>
<td>83</td>
</tr>
<tr>
<td>18</td>
<td>81</td>
<td>61</td>
</tr>
<tr>
<td>24</td>
<td>71</td>
<td>45</td>
</tr>
<tr>
<td>30</td>
<td>64</td>
<td>41</td>
</tr>
</tbody>
</table>

Summary- It’s Time for New Guidelines!

- New epidemiologic data convincingly and consistently demonstrate an association of fasting serum P with a variety of adverse clinical outcomes including CKD progression and mortality.

- Data to support current guideline recommendations such as dietary intervention OR phosphate binders ALONE are limited at best although data exist to show effect of combined treatment with both diet + binders.

- Physiology of Na-dependent and Na-Independent P absorption is poorly understood and an immediate need for research to determine if any adverse effect on health

- Current ACTUAL care of patients with CKD most commonly involves dietary P restriction and provision of calcium containing P binders

- NEW guidelines are warranted to address the uncertainty and potential harm associated with current recommendations (diet + binders) in CKD. Many additional questions remain....