Case Presentation

HPI: 28 yo man with h/o schizophrenia/bipolar disorder, ETOH abuse and h/o ETOH pancreatitis who was admitted to BHC after being hit by a train. He suffered multiple injuries including non-salvageable damage to his RLE requiring a R-BKA. He also suffered rib fractures, and multiple facial fractures for which he underwent surgery. On HD # 25, he was transferred to inpatient rehab for further care.

Routine labs during his rehab stay revealed hyperphosphatemia, with a Phosphate level of 5.3 initially, followed by a Phosphate level of 7.8. Renal consult was called for further evaluation.

The patient denied muscle pains, N/V, abdominal pain. Review of his medications showed he had received phosphate-based supplementations early in his hospital stay, but none recently. Denied taking any OTC supplements or vitamins. No phosphate based laxative use.
• **PMH:**
  • Schizophrenia vs Bipolar disorder
  • ETOH abuse with h/o withdrawal seizures
  • h/o alcoholic pancreatitis

• **PSH:**
  • Multiple facial surgeries, skin graft harvesting
  • RLE BKA

• **All:** NKDA
• **Medications:**
  - Baclofen 10mg PO q12
  - Clonazepam 0.5mg PO TID
  - Colace 100mg PO TID
  - Lovenox 30mg Sq q12
  - Nexium 40mg PO daily
  - Gabapentin 900mg PO q8
  - Methadone 95mg PO daily
  - Quetiapine 50mg PO qhs
  - PRNs: Tylenol, Dilaudid, Ativan, Quetiapine

• **SH:** Living in a mental health shelter in Queens PTA. Attended a Methadone program. H/o polysubstance abuse including ETOH, heroin, cocaine.

• **FH:** No family h/o nephrolithiasis, kidney disease or endocrine disorders including parathyroid disease.
• **Physical Exam:**
  • VS: Afebrile, BP 114/54, HR 72, RR 18, O2 sat 100% RA
  • Gen: sitting in wheelchair in NAD
  • HEENT: well-healed incision on forehead, no pallor or icterus
  • Chest: CTAB
  • CV: RRR, nl s1s2, no murmurs appreciated
  • Abd: soft, nt/nd, +BS
  • Ext: WWP, s/p R-BKA, no edema on LLE
## Labs

<table>
<thead>
<tr>
<th>Date</th>
<th>Na</th>
<th>K</th>
<th>Cl</th>
<th>CO2</th>
<th>BUN</th>
<th>Cr</th>
<th>Gluc</th>
<th>Ca</th>
<th>Phos</th>
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<td>119</td>
<td>8.5</td>
<td>3.6</td>
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<td>139</td>
<td>4.1</td>
<td>101</td>
<td>33</td>
<td>8</td>
<td>0.5</td>
<td>99</td>
<td>8.1</td>
<td>5.3</td>
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<tr>
<td>4/23</td>
<td>143</td>
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<td>103</td>
<td>32</td>
<td>10</td>
<td>0.6</td>
<td>82</td>
<td>8.5</td>
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<td>4.3</td>
<td>107</td>
<td>31</td>
<td>8</td>
<td>0.6</td>
<td>77</td>
<td>8.8</td>
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<tr>
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<td>4.1</td>
<td>107</td>
<td>30</td>
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<td>0.7</td>
<td>102</td>
<td>9.0</td>
<td>5.3</td>
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<td>6/20</td>
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<td>4.4</td>
<td>104</td>
<td>27</td>
<td>13</td>
<td>0.8</td>
<td>80</td>
<td>9.2</td>
<td>4.6</td>
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<table>
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<tr>
<th>Date</th>
<th>25-OH VitD</th>
<th>PTH</th>
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<tr>
<td>4/23</td>
<td>-----</td>
<td>3.2</td>
</tr>
<tr>
<td>4/28</td>
<td>-----</td>
<td>10.1</td>
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<tr>
<td>5/11</td>
<td>12</td>
<td>7.7</td>
</tr>
<tr>
<td>6/20</td>
<td>29</td>
<td>13.8</td>
</tr>
</tbody>
</table>

CPK: 507 then 320
Albumin 3.8
IGF-1: wnl
Labs

UA: SG <1.005, pH 6.5, negative blood, negative protien, no RBCs or WBCs

Urine Phos 26.9
U Cr 41.6
FePhos 7%

Urine:

Cr 41.6
K 37
Na 83
Cl 93

24 hr urine (2.6 L):

Cr 1.18
Na 138mmol
K 65 mmol
Cl 114 mmol

U Ca 11.8mg/dl
Phosphate Metabolism

• In the steady state, the serum phosphate concentration is primarily determined by the kidneys ability to excrete dietary phosphate
• This typically occurs up to an intake as high as 4 g/d (130mmol/d)
• The response if mediated in part by a direct effect of mild hyperphosphatemia to diminish proximal tubular reabsorption
  • Via inhibition of Na+-phosphate cotransporters in the luminal membrane that allow reabsorption of filtered phosphate
• Hyperphosphatemia results from one of three majors causes:
  • Increased phosphate load (exogenous or endogenous)
  • Renal failure
  • Primary increase in proximal phosphate reabsorption
Increased Phosphate Load

• Any cause of marked tissue breakdown can lead to the release of intracellular phosphate into extracellular fluid
  • Tumor lysis
  • Rhabdomyolysis
  • Hemolysis
  • Massive transfusions
• Exogenous Phosphate
  • Laxatives – Fleet Phospho-soda
  • Acute phosphate nephropathy can result
Increased Tubular Reabsorption of Phosphate:

- Hypoparathyroidism
- Acromegaly
- Bisphosphonates
- Vitamin D toxicity
- Familial tumoral calcinosis

Pseudohyperphosphatemia:

- Tourniquet effect
- Interference with analytical methods may occur in patients with hyperglobulinemia, hyperlipidemia, hemolysis, and hyperbilirubinemia
• The type II sodium phosphate cotransporters (SLC34) are responsible for the majority of physiologic phosphate transport
• 3 members of the family: NaP-IIa (SLC34A1), NaP-IIb (SLC34A2), NaP-Iic (SLC34A3)

*J Pharm Sci* 2011
Hypoparathyroidism

- PTH blocks the Na-Pi co-transporters in the proximal tubule

- Decreased PTH will lead to increased proximal reabsorption of phosphate

- Patients typically present with hypocalcemia 2/2 decreased bone resorption and decreased hydroxylation of Vit D (leading to less absorption of Ca+ from the gut)
Hypoparathyroidism, cont’d

- Most commonly observed following neck surgery
- Autoimmune destruction
- Congenital syndromes of parathyroid dysgenesis (DiGeorge syndrome, eg)

- Patients typically have uniformly increased bone mineral density
- Bone biopsy specimens show greater cancellous bone volume, trabecular width, and cortical width compared with age- and sex- matched controls
Treatment of Hypoparathyroidism

• Standard treatment consists of oral calcium and Vitamin D supplementation
• However, maintaining serum calcium levels can be a challenge
• Concerns exist regarding hypercalciuria and ectopic calcifications that can be associated with such treatment
• Hypoparathyroidism is the only classic endocrine deficiency disease for which the missing hormone, PTH, is not yet an approved treatment
• Two formulations of PTH are currently being studied (both administered by subcutaneous injection):
  • Teriparatide = human PTH (1-34)
  • PTH (1-84) = the full length molecule
PTH (1-34): Teriparatide

- Randomized, controlled trial of 27 patients with hypoparathyroidism (ages 18-70)
- The major etiologies of hypoparathyroidism were post-surgical, sporadic calcium receptor mutations, and idiopathic
- Patients were randomized to:
  - Twice daily PTH (1-34)
  - Standard therapy with Calcitriol q12 and Calcium supplementation
  - Doses were adjusted in both groups to maintain serum calcium level within normal limits
- Primary outcome was serum and urine calcium levels
- Secondary outcomes included measures of BMD, phosphorus levels
- Subjects were treated and followed for 3 years

*J Clin Endo Metab* 2003
Over 3 years, both PTH and calcitriol were effective in maintaining the mean serum calcium level close to normal (bottom graph).

The mean urinary calcium excretion was higher in the Calcitriol group (8.2 mmol/24hr) compared to the PTH group (5.8 mmol/24hr), with normal range of 1.25-6.25 mmol/24hr.
• PTH resulted in a significant increase in the markers of bone turnover in both serum and urine
• Markers rose gradually with PTH therapy, and peaked at 2.5 yrs
• BMD not significantly different between groups
• FGF-23 is a phosphaturic hormone synthesized in bone (by osteoblasts and osteocytes) in response to increased dietary phosphate
• FGF-23 decreases serum Pi levels through inhibition of NaP-Iia contransporters
• FGF-23 also acts to suppress 1-α-hydroxylase resulting in decrease in 1,25-dihydroxyvitamin D, leading to decreased intestinal absorption on Pi
• FGF-23 needs to bind to Klotho in the distal tubule in order to increase its affinity for FGF-receptor
Disorders of Decreased FGF-23 level

- Familial Tumoral Calcinosi (FTC)
  - A rare, autosomal recessive disease that results in hyperphosphatemia and ectopic calcifications
  - Results from loss-of-function mutations of FGF-23

- GALNT3 mutation
  - GALNT3 gene encodes the glycosyl transferase ppGantase 3, which results in O-glycosylation of FGF23 and results in decreased susceptibility to proteolytic degradation
  - Mutations result in decreased levels of intact FGF23, but increased levels of the processed, C-terminal FGF23 fragment

- Mutations in FGF-23 or Klotho (Kl) genes

- Serum calcium and PTH levels are usually normal
  - Increased levels of calcitriol
  - Normal serum calcium levels in setting of hyperphosphatemia leads to elevated Ca/Phos product, leading to ectopic calcifications
Renal expression of NaPi-2a and serum levels of phosphate in Kl-knockout mice:

- Compared with WT mice, Kl-/- mice exhibit increased renal expression of NaPi-2a and hyperphosphatemia
- The hyperphosphatemia is observed by 3 weeks of age and their serum phosphate levels remain high for their entire lifespan
In addition to the known phosphaturic effects of PTH and FGF23/Klotho, there appears to be an intestinal phosphatonin that is released from the intestine in the setting of a phosphate load, that leads to phosphaturia in the absence of high serum phosphate levels.
Long term effects

• It is known that abnormalities in calcium and phosphate metabolism in people with abnormal renal function are directly related to the burden of vascular disease in this population
  • Calcification of the vasculature has been associated with increased rates of CAD, PVD, and valvular disease in patients with CKD
• In patients without CKD, vascular calcification has been viewed as the result of atherosclerosis and not as a primary calcifying process in vessels
• Recently, some studies have shown that higher phosphate levels, even within the normal range, are associated with abnormal vascular phenotypes in patients with normal renal function
  • Increased carotid intima-media stiffness and arterial stiffness
Table 1

Studies reporting prediction of cardiovascular outcomes or mortality by serum phosphate levels within the normal range. Pi, phosphate; OR, odds ratio; HR, hazard ratio; SD, standard deviation; NS, non-significant.

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Population</th>
<th>N</th>
<th>F/U</th>
<th>Outcome</th>
<th>Adjusted risk increase (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kestenbaum (2005)</td>
<td>Patients with early CKD; median estimated creatinine clearance 41 ml/min</td>
<td>3490</td>
<td>2 yrs</td>
<td>Mortality</td>
<td>HR 1.32 (1.09–1.61) for Pi 1.13–1.29 mM vs. 0.81–0.97 mM</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Myocardial infarction</td>
<td>HR 1.35 (1.09–1.66) for each 0.32 mM Pi increase</td>
</tr>
<tr>
<td>Tonelli (2005)</td>
<td>Post myocardial infarction statin trial</td>
<td>4127</td>
<td>5 yrs</td>
<td>Mortality</td>
<td>HR for each 0.32 mM Pi increase:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>New symptomatic heart failure</td>
<td>1.27 (1.02–1.58)</td>
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<td></td>
<td></td>
<td></td>
<td>Fatal or nonfatal myocardial infarction</td>
<td>1.22 (0.95–1.57, NS but p = 0.02 for linear trend)</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Composite outcome; myocardial infarction, angina, stroke, TIA, heart failure or peripheral vascular disease</td>
<td>1.24 (1.00–1.53)</td>
</tr>
<tr>
<td>Dhingra (2007)</td>
<td>Healthy community population without kidney disease or symptomatic cardiovascular disease; mean age 44</td>
<td>3368</td>
<td>16 yrs</td>
<td>Composite outcome; myocardial infarction, angina, stroke, TIA, heart failure or peripheral vascular disease</td>
<td>HR 1.31 (1.05–1.63) for each 0.32 mM (1 mg/dl) Pi increase:</td>
</tr>
<tr>
<td>Foley (2008)</td>
<td>Healthy young adults; mean age 25</td>
<td>3015</td>
<td>15 yrs</td>
<td>Likelihood of greater coronary calcification score measured on CT 15 years later</td>
<td>Adjusted OR 1.17 (1.01–1.34) for each 0.16 mM increase in baseline Pi</td>
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<tr>
<td>Foley (2008)</td>
<td>Community cohort</td>
<td>13,822</td>
<td>13 yrs</td>
<td>Coronary heart disease</td>
<td>HR for Pi quintile 5 versus quintile 1:</td>
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<td>Stroke</td>
<td>1.03 (0.88–1.21, NS)</td>
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<td></td>
<td></td>
<td></td>
<td>Death</td>
<td>1.28 (0.97–1.70, NS)</td>
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<td></td>
<td></td>
<td></td>
<td>Cardiovascular mortality</td>
<td>1.35 (1.16–1.57)</td>
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<td>Chonchol (2009)</td>
<td>Type II diabetics in a blood pressure trial</td>
<td>950</td>
<td>5 yrs</td>
<td>Cardiovascular mortality</td>
<td>HR 4.25 (1.15–16.65) for time-averaged Pi</td>
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<tr>
<td>Foley (2009)</td>
<td>Healthy young adults; mean age 25</td>
<td>4055</td>
<td>5 yrs</td>
<td>LVH on echo 5 years later</td>
<td>OR per SD Pi increase 1.30 (1.10–1.54)</td>
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<tr>
<td>Larsson (2010)</td>
<td>Community cohort; males only</td>
<td>2176</td>
<td>30 yrs</td>
<td>Cardiovascular mortality</td>
<td>HR 1.10 (1.02–1.18) per SD Pi increase</td>
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<tr>
<td>Abramowitz (2010)</td>
<td>Medical outpatients with measures of creatinine, Pi and alkaline phosphatase</td>
<td>10,743</td>
<td>7 yrs</td>
<td>Mortality</td>
<td>HR 1.08 (1.01–1.15) per SD phosphate increase</td>
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<td></td>
<td></td>
<td>HR 1.29 (1.07–1.55) for top quartile versus bottom quartile</td>
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Framingham Offspring Study

- Included patients from the Framingham Heart Study who had routine serum phosphorous and calcium levels measured between 1979-1982
- Excluded patients with CVD (coronary heart disease, PVD, cerebrovascular disease, or heart failure) and/or impaired renal function (eGFR <60 ml/min)
- A total of 3368 patients were included (51% women)
- Patients in the FHS were under continuous surveillance for CVD:
  - Incident CVD was defined as fatal or nonfatal MI, angina, cerebrovascular events (stroke or TIAs), PVD, or CHF
- Over a follow-up period of 20 years, 524 participants experienced a first CVD event:
  - 138 MIs, 93 cerebrovascular events, 18 SCDs, 39 CHF
### Table 3. Cox Proportional Hazard Models Examining the Relations of Serum Phosphorus and Serum Calcium Levels to Incidence of CVD

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Incident CVD, No.</th>
<th>Subjects at Risk, No.</th>
<th>Age- and Sex-Adjusted Model</th>
<th>Multivariable Model 1</th>
<th>Multivariable Model 2†</th>
<th>Multivariable Model 3‡</th>
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<tr>
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<td>Serum Phosphorus Level</td>
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<tr>
<td>2</td>
<td>140</td>
<td>868</td>
<td>1.10 (0.87-1.39)</td>
<td>1.23 (0.95-1.59)</td>
<td>1.41 (1.04-1.90)</td>
<td>1.87 (1.20-2.89)</td>
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<tr>
<td>3</td>
<td>129</td>
<td>915</td>
<td>1.08 (0.84-1.37)</td>
<td>1.27 (0.97-1.67)</td>
<td>1.34 (0.98-1.83)</td>
<td>1.51 (0.97-2.37)</td>
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<td>4</td>
<td>118</td>
<td>770</td>
<td>1.32 (1.02-1.71)</td>
<td>1.55 (1.16-2.07)</td>
<td>1.47 (1.05-2.06)</td>
<td>2.01 (1.27-3.17)</td>
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<td>P value for trend</td>
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<td>Serum Calcium Level</td>
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<td></td>
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</tr>
<tr>
<td>2</td>
<td>142</td>
<td>1023</td>
<td>0.83 (0.66-1.06)</td>
<td>0.86 (0.66-1.12)</td>
<td>0.82 (0.61-1.12)</td>
<td>1.10 (0.78-1.90)</td>
</tr>
<tr>
<td>3</td>
<td>102</td>
<td>698</td>
<td>0.88 (0.68-1.14)</td>
<td>0.95 (0.71-1.26)</td>
<td>0.92 (0.66-1.29)</td>
<td>1.41 (0.90-2.23)</td>
</tr>
<tr>
<td>4</td>
<td>148</td>
<td>831</td>
<td>1.03 (0.82-1.31)</td>
<td>1.06 (0.80-1.40)</td>
<td>1.06 (0.77-1.47)</td>
<td>1.20 (0.76-2.67)</td>
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<tr>
<td>P value for trend</td>
<td>.59</td>
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</table>

*HR for CVD (95% CI)*

Graph: Hazard Ratio for CVD vs. Serum Phosphorus Level, mg/dL
Uppsala Longitudinal Study of Adult Men

- Ongoing population-based study aiming to identify risk factors for cardiovascular disease
- Community-based cohort study of 2,176 men, mean age 50.1 years
- Mean follow-up time of 29.8 years
- Measured serum Ca, Phos, eGFR at age 50
- Followed through December 2002
- Primary Endpoint: cardiovascular death
- During follow-up, 1009 men died
  - 466 of cardiovascular disease
  - 543 of non-cardiovascular disease
• Serum Pi and Ca-Phos were predictors of both cardiovascular mortality and total mortality (about 10% higher risk)

• Serum Calcium was predictor of total mortality and non-cardiovascular mortality (about 10% higher risk)

• In subset of patients with eGFR > 90 and in subset of patients with normal baseline calcium and phosphate levels, the results were consistent
Fig. 2. Potential causative mechanisms linking the phosphate axis with atherosclerotic vascular disease. See text for details. ROS, reactive oxygen species.
The Heart and Soul Study

• Observational study of 833 patients with stable coronary artery disease, recruited from 12 outpatient clinics in the San Francisco Bay area

• Fasting serum and plasma samples were obtained at the baseline visit and frozen; later, measured FGF-23 levels (as well as several other markers of mineral metabolism – including ucMGP and fetulin-A)

• Outcomes – composite of MI, stroke, TIA, heart failure as a CVD event
  • Annual phone interviews inquiring about hospitalizations, cardiac procedures, or death

Annals of Internal Medicine 2010
Of 833 participants, there were 183 CVD events over median f/u of 5.2 yrs.

- 220 deaths over median 6.0 yrs
- When FGF23 was evaluated as a continuous predictor, each doubling in FGF23 level was associated with a 41% higher mortality risk and 24% higher CVD event risk.

- 22% of the participations had moderate CKD (eGFR < 60ml/min)
- Association with CKD or death was the similar, regardless of the presence of absence of CKD.
In conclusion...

- Although, hyperphosphatemia and elevated FGF-23 levels appear to be associated with high rates of CVD and mortality even in non-CKD populations, a causal relationship is still not known.
- Further studies are needed to elucidate the potential link between phosphate homestasis and vascular risk.
Thank you