Mineral and bone disease associated with CKD

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THE TRADE-OFF HYPOTHESIS

GFR (ml/min)

PO₄ (mg %)

Ca (mg %)

PTH (units)

TIME (YEARS)
MEDIAN VALUES OF SERUM CALCIUM, PHOSPHORUS & PTH BY GFR

Data from 1814 pts enrolled in the Study for the Evaluation of Early Kidney Disease (SEEK)
1 hyperparathyroid osteitis fibrosa cystica (high turnover bone disease)
2 osteomalacia
3 mixed
PHOSPHATE TRANSPORT

Diet/Intestine → Extracellular Fluid → Proximal Tubule Cells → Tubule Lumen

Diffusion

P_{i} → P_{i} → P_{i}

NPT2b → sFRP-4 → NaPi2c

NHERF 1

PTH R

NaPi2c → NPT2a
[Diagram showing regulatory interactions involving phosphorus, serum PO₄, 1,25(OH)₂D, PTH, FGF23, NaPi, and 1α-OHase.]
FGF23 LEVELS IN CKD
Most of the observational data relating FGF-23 to adverse clinical outcomes have used the carboxy-terminal assay (RU/ml), whereas many recent studies addressing change in FGF-23 levels over time have reported intact FGF-23 values (pg/ml).

It remains unclear which assay might be preferable for serial measurements in the setting of CKD. AJKD 2013;62:457

Parental iron administration has been associated with increase in FGF-23 in persons with normal renal function (KI 2010;77:845)
FGF23: 32 kD, 251 AA
synthesized and secreted by osteocytes in response to raised serum P and calcitriol

**Overexpression of FGF23:**
- ↓ P, ↓ Ca
- ↓ 1,25(OH)$_2$D
- ↑ PTH
- rickets, osteomalacia

**Knock out of FGF23:**
- ↑ P, ↑ Ca
- ↑ 1,25(OH)$_2$D
- ↓ PTH
- Soft tissue calcifications, hypoglycemia, hypoinsulinemia, ↑ insulin sensitivity
- shorten lifespan (die at ~ 13 weeks)
- Most of the phenotype rescued by double knock out of FGF-23 and 1α OH-ase
- Features similar to human tumoral calcinosis
The Fates
There are three conjoined Fates, robed in white, whom Erebus begot on Night: by name Clotho, Lachesis, and Atropos. Of these, Atropos is the smallest in stature, but the most terrible.

Zeus, who weighs the lives of men and informs the Fates of his decisions can, it is said, change his mind and intervene to save whom he pleases, when the thread of life, spun on Clotho's spindle, and measured by the rod of Lachesis, is about to be snipped by Atropos's shears.

Other held another custom that Zeus himself is subject to the
Japanese group exploring aging mechanisms fortuitously discovered gene that when disrupted caused mouse to age faster and die earlier, when overexpressed slowed aging and extended lifespan

Klotho knock out:
short lifespan, growth retardation, cognition impairment, adynamic bone disease, osteoporosis, soft tissue and vascular calcification, ↑ serum Ca and P, ↑ plasma calcitriol, ↓ PTH, ↑ FGF23 levels, hypogonadotropic hypogonadism, skin & muscle atrophy, emphysema, senescent changes in heart, lungs, hearing loss, early thymic involution, hypoglycemia, hypoinsulinemic, ↑↑ insulin sensitivity, premature death around 9 weeks of age

Nat Rev Nephrol 2013;9:650
DISTURBANCE OF MINERAL METABOLISM AND MORTALITY

**Relative Risk of Death**

- **Plasma iPTH (pg/mL)**
  - < 150
  - 150-300
  - 300-600
  - > 600

- **Corrected Serum Calcium (mg/dL)**
  - < 8.0
  - 8.0-8.5
  - 8.5-9.0
  - 9.0-9.5
  - 9.5-10.0
  - 10.0-10.5
  - 10.5-11.0
  - > 11.0

- **Ca x P (mg²/dL²)**
  - < 30
  - 30-35
  - 35-40
  - 40-45
  - 45-50
  - 50-55
  - 55-60
  - 60-65
  - 65-70
  - 70-75
  - > 75

- **Serum Phosphorus (mg/dL)**
  - < 3.0
  - 3.0-4.0
  - 4.0-5.0
  - 5.0-6.0
  - 6.0-7.0
  - 7.0-8.0
  - > 9.0

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The median fibroblast growth factor 23 (FGF-23) level within the lowest FGF-23 quartile (74 RU/mL) served as the referent value (hazard=1.0). Tick marks on the x-axis indicate individual observations at corresponding levels of FGF-23. The solid black line represents the multivariable-adjusted hazard of mortality as a function of the measured (nontransformed) FGF-23 level. The dashed lines indicate the 95% confidence intervals. (JAMA 2011;305:2432)
American College of Rheumatology Guidelines for Screening, Treatment, and Management of Lupus Nephritis

BEVRA H. HAHN,1 MAUREEN A. McMAHON,1 ALAN WILKINSON,5 W. DEAN WALLACE,1 DAVID I. DAIKH,2 JOHN D. FITZGERALD,3 GEORGE A. KARPOUZAS,3 JOAN T. MERRILL,3 DANIEL J. WALLACE,4 JINOOS YAZDANY,2 ROSALIND RAMSEY-GOLDMAN,5 KARANDEEP SINGH,1 MAZDAK KHALIGHI,1 SOO-IN CHOI,1 MANEESH GOGIA,1 SUZANNE KAFAJA,1 MOHAMMAD KAMGAR,3 CHRISTINE LAU,1 WILLIAM J. MARTIN,1 SEFALI PARikh,1 JUSTIN PENG,1 ANJAY RASTOGI,1 WEILING CHEN,1 AND JENNIFER M. GROSSMAN1

Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis

George K Bertsias, Maria Tektonidou, Zahir Amoura, et al.

Ann Rheum Dis 2012 71: 1771-1782 originally published online July 31, 2012

Chapter 12: Lupus nephritis


TTP & Goodpasture mortality
95% → <10%
w/o wise men’s guidelines
Guidelines for lupus nephritis—more recommendations than data?
KDIGO GUIDELINE FOR CKD-MBO

KDIGO (kidney disease improving global outcomes) is a global non-profit foundation dedicated to improving the care and outcomes of kidney disease patients worldwide (private corporation funded by industry)

KDIGO: 61 guideline recommendations: 2 (3%) 1A, 31 (51%) 2C or 2D, 12 (20%) not graded

4.3.1
In patients with CKD stages 1–2 with osteoporosis and/or high risk of fracture, as identified by WHO criteria, we recommend management as for the general population (1A).

4.3.5
In children and adolescents with CKD stages 2–5D and related height deficits, we recommend treatment with recombinant human growth hormone when additional growth is desired (1A).
PHOSPHORUS BALANCE

~ 1000 mg/day of P absorption  =  ~ 7000 mg/week intake
~ 1000 mg/HD of P removed  =  ~ 3000 mg/week removal

~ 4000 mg/week + balance

P from plants usually in form of phytate, poorly absorbed (humans lack enzyme phytase)

P from meat easily absorbed
P from milk not easily absorbed
P from processed food almost completely absorbed

More than ½ of pts with advanced CKD who were placed on very low protein diet and P restricted diet for 5 y developed moderate to severe osteoporosis, even those with normal bone turnover and despite reversal of 2° HPTH. (AJKD 2010;55:941)
KDOQI: data are insufficient to strongly endorse dietary P restriction as the primary intervention for management of CKD-MBD
4 g of CaCO3 contains 1.6 g of calcium, whereas 4 g of acetate 1.0 g.

<table>
<thead>
<tr>
<th>Phosphate binder</th>
<th>RPBC by g of compound listed in available product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium carbonate (index value)</td>
<td>1.0</td>
</tr>
<tr>
<td>Calcium acetate</td>
<td>1.0</td>
</tr>
<tr>
<td>Magnesium carbonate</td>
<td>1.7</td>
</tr>
<tr>
<td>(anhydrous weight, Magnebind)</td>
<td></td>
</tr>
<tr>
<td>“Heavy” magnesium carbonate</td>
<td>1.3</td>
</tr>
<tr>
<td>(hydrated weight, OsvarRen)</td>
<td></td>
</tr>
<tr>
<td>Aluminum hydroxide</td>
<td>1.5</td>
</tr>
<tr>
<td>Aluminum carbonate</td>
<td>1.9</td>
</tr>
<tr>
<td>Sevelamer (carbonate or hydrochloride)</td>
<td>0.75</td>
</tr>
<tr>
<td>Lanthanum carbonate</td>
<td>2.0$^a$</td>
</tr>
</tbody>
</table>
There was a significant decrease in risk of hypercalcemia with sevelamer and lanthanum in comparison to calcium salts.

There was a significant increase in risk of gastrointestinal events with sevelamer in comparison to calcium salts.

There was a significantly greater end-of-treatment serum phosphorus level with sevelamer in comparison to calcium salts.

There was a significantly greater end-of-treatment PTH level with sevelamer compared with calcium salts.

Sevelamer substantially impaired absorption of calcitriol, while lanthanum had no effect. (?interference with fat soluble vitamins)
Colestilan
nonabsorbed anion exchange resin used to decrease cholesterol

Nicotinamide (Niacine)
not a P-binder, inhibits NaPi2b and NaPi2a
12 weeks of Rx: P 6.9→ 5.4, LDL 78.9→70.1, HDL 47.4→67.2
advantage: may take extended release pill at bedtime
side effects: ↓ Plts, n/v, pruritus, hives, flushing, ↑ uric acid
Semin Dialysis 2008;21:203

Trivalent iron
complexed as simple salt (citrate, chloride) or cross linked dextran or polynuclear iron hydroxyde.
sucroferric oxyhydroxide

KI 2014, JASN 2014

ferric citrate
At any given time, ~10–20% of the skeleton undergoes remodeling, and a typical remodeling cycle can take up to 3–6 months.
TMV CLASSIFICATION
NORMAL BONE
Ultra high-resolution peripheral quantitative computed tomography (HRpQCT) of the distal radius (middle) and transiliac crest bone biopsy (right).

The red arrow represents trabecular bone microarchitecture, which was unremarkable. The black arrow represents cortical bone, which is severely deteriorated.
Tetracycline is buried within mineralized osteoid (tetracyclin will deposit in the bone where calcium is being deposited).
2 labels can be used, tetracycline stains yellow, demeclocycline yellow/orange

80-90% of matrix is mineralized, 10-20% is osteoid
BONE HISTOLOGY vs PTH IN HD PATIENTS

Total # of pts 97

- low turnover 58 pts
- normal turnover 3 pts
- high turnover 36 pts

iPTH

- < 150
- 150-300
- > 300

# of patients
SECONDARY HYPERPARATHYROIDISM

rugger jersey spine
RENAL OSTEODYSTROPHY IN BLACKS AND WHITES WITH ESRD

Bone turnover:
- Low: B: 2/3, W: 1/3
- Normal: B: 2/3, W: 1/3
- High: B: 1/3, W: 1/3

Bone volume:
- Low: B: 2/3, W: 1/3
- Normal: B: 1/3, W: 1/3
- High: B: 1/3, W: 1/3

Cortical thickness:
- Low: B: 3/4, W: 1/2
- Normal: B: 1/3, W: 1/3
- High: B: 1/3, W: 1/3

J Bone Miner Res 2011;26:1368
Although similar PTH reference intervals are provided by most manufacturers, between-method differences for a single patient specimen ranged from 1.4 - 4.2-fold. These differences were sufficient to have treatment implications for 79% of the patients. 

Ann Clin Biochem 2012;49:63
If we adopt the recommended policy of four PTH measurements a year, this assess the concentration of this hormone for 0.003% of the patient's "clinical" year. It is an act of optimism (or folly) to imagine that these precious 16 minutes of comprehension will guide us adequately when making therapeutic decisions over the remainder of the year.

We believe that until intact PTH assays actually measure intact PTH, until pre analytic conditions and assay calibration are universally standardized, and until better evidence links PTH to skeletal or CVS endpoints in CKD, it is hard to support continued measurement of PTH according to current recommended practice.  

CJASN 2013;8:299
cholesterol

7-Dehydrocholesterol
pro-vitamin D3

vitamin D3 (cholecalciferol)

vitamin D2 (ergocalciferol)
potency <1/3 of D3

ergosterol
pro-vitamin D2
Hepatic production of 25(OH)D is inhibited by 1,25(OH)2D.

Low serum calcium and phosphorus, high PTH and calcitonin stimulate 1-a hydroxylase.

FGF-23 inhibits 1-hydroxylase and increases 24-hydroxylase.
Active vitamin D also increases 24-hydroxylase expression.

15 minutes in the sun in a bathing suit in July produces in a light skin individual 10,000-20,000 IU of vitamin D  (CJASN 2008;3:1535)

D2 is much less efficiently converted to 25(OH)D than D3.
Vitamin D deficiency soars in the U.S., study says

New research suggests that most Americans are lacking a crucial vitamin.

Mar 23, 2009 | By Jordan Lite

Three-quarters of U.S. teens and adults are deficient in vitamin D, the so-called “sunshine vitamin” whose deficits are increasingly blamed for everything from cancer and heart disease to diabetes, according to new research.

The trend marks a dramatic increase in the amount of vitamin D deficiency in the U.S., according to findings set to be published tomorrow in the Archives of Internal Medicine. Between 1988 and 1994, 45 percent of 16,883 people (who were examined as part of the federal government’s National Health and Nutrition Examination Survey) had 30 nanograms per milliliter or more of vitamin D, the blood level a growing number of doctors consider sufficient for overall health; a decade later, just 23 percent of 13,369 of those surveyed had at least that amount.

The slide was particularly striking among African Americans: just 3 percent of 2,149 blacks sampled in 2004 were found to have the recommended levels compared with 12 percent of 5,362 sampled two decades ago.

"We were anticipating that there would be some decline in overall vitamin D levels, but the magnitude of the decline in a relatively short time period was surprising," lead researcher Dr. Howard M. Sesso of Harvard Medical School said. "The decline was even more dramatic among African-Americans, who are at a particularly high risk for vitamin D deficiency due to darker skin and less sun exposure."

Why are these widespread vitamin D deficiencies of such great concern? Because research conducted ...

Vitamin D and Health - Harvard School of Public Health
www.hsph.harvard.edu/nutritionsource/vitamin-d/
Vitamin D–binding protein is binds 85 to 90% of total circulating 25-OH D. The non–vitamin D–binding protein fraction (bioavailable 25-OH D) consists of albumin-bound 25-OHD (10 to 15% of total 25-hydroxyvitamin D), with less than 1% of total 25-hydroxyvitamin D in the free form.

Clinical assays measure the level of total 25-hydroxyvitamin D without distinguishing fractions bound to carrier proteins.

With similar PTH levels blacks had significantly lower total 25-OH vitamin D compared to whites (A), but they had similar levels of bioavailable 25-OH vitamin D (B).

NEJM 2013;369:1991
VITAMIN D SUPPLEMENTATION IN CKD

To date there are no well designed randomized controlled trials or large observational cohort studies that evaluate whether administration of nutritional vitamin D in patients with CKD improves patient-centered clinical outcomes, such as overall mortality, cardiovascular disease, or infection.

Despite the lack of evidence, KDOQI and KDIGO recommended:

if 25-OHD <15 ng/mL
50,000 units of ergocalciferol once a week for 4 weeks followed by the same dose once a month for 4 months,

if 25-OHD 20-30 ng/mL
50,000 units once a month for 6 months.

These guidelines have been based on extrapolation of data from the general population and have been largely opinion based rather than evidence based.
CALCIUM SENSING RECEPTOR

**Gain of function**
- Parathyroid cell
- CaSR
- Calcimimetics
- Ca$^{2+}$
- PTH

**Loss of function**
- Parathyroid cell
- CaSR
- Calcilytics
- Ca$^{2+}$
- PTH

**Diseases (Gain)**
- Autosomal dominant hypoparathyroidism (CaSR constitutively activating mutations)
- Autoimmune hypocalcemia (activating anti-CaSR antibodies)

**Diseases (Loss)**
- Familial hypocalciuric hypercalcemia (CaSR inactivating mutations)
- Autoimmune hypercalcemia (blocking anti-CaSR antibodies)

**Therapy (Gain)**
- Calcimimetics for secondary hyperparathyroidism

**Therapy (Loss)**
- Calcilytics for osteoporosis?
Conceptually, drugs that act on the CaSR could inhibit PTH secretion by either lowering the threshold of receptor activation in response to extracellular calcium or by directly activating the receptor through binding to the extracellular domain.

Cinacalcet acts as an allosteric modulator of the CaSR, potentiating the action of extracellular calcium by lowering the threshold for receptor activation, resulting in an inhibition of PTH secretion and production.

AMG 416 directly activates the CaSR with activity in the presence or absence of ambient serum calcium, a mechanism of action distinct from that of cinacalcet hydrochloride.
AMG 416 (VELCALCETIDE)

Single iv dose, HD patients
7,076 incident patients (4,947 hemodialysis, 2,129 peritoneal dialysis).

In adjusted Cox proportional hazards models, patients who achieved guideline targets in all 4 quarters did not have a survival advantage over patients who never achieved target ($P > 0.1$ for calcium, phosphate, and iPTH).

Conclusions: Our findings do not support the use of KDOQI bone mineral guideline achievement as a quality measure for dialysis care. Prospective studies with longer term follow-up are needed to define the optimal cutoff values for calcium, phosphate, and iPTH and assess the effect of guideline implementation on patient survival.
High or low calcium, phosphorus, PTH, FGF23 are all blamed for increased mortality but no expert can tell us what is the optimal level for each of these markers.

No RTC has ever been done to show that intervention to lower PTH, calcium, phosphorus or FGF23 improve mortality.

High phosphorus is most likely the main culprit but we do not know what is the best way to bring it to optimal level which we also do not know what should be.

We cannot distinguish intimal from medial calcifications and treatment of vascular calcifications is based on the assumption that they are harmful (are intimal calcifications harmful?)
CONCLUSION

No one question that extreme PTH levels <100, >1000 need correction, but most patients had levels between these extremes. 
nonoxidized vs. oxidized PTH
How we can accept that event over 16 minutes determines decision for 525600 minutes of patients’ life

Likewise in blaming FGF23 as a major uremic toxin, why we cannot understand that some elevations may be physiologic and not maladaptive

We define vitamin D deficiency based on flawed assay

There are no RCT or large observational cohort studies that evaluate whether administration of nutritional vitamin D in patients with CKD improves mortality, cardiovascular disease, infection or overall patient-centered clinical outcomes, yet KDIGO generously offers recommendations
When practice guidelines promote therapeutic strategies without sufficient evidence of effectiveness or harms, overtreatment and widespread inappropriate use of medications, services, or devices may occur. Accordingly, guidelines may recommend health interventions that do not actually improve population outcomes or the quality of care, unnecessarily increase health care expenditure, and may even harm individuals who might be expected to receive small or negligible treatment benefit.

Based on the available cohort data and the absence of randomized controlled trials, the evidentiary basis for current clinical guideline–recommended targets of serum phosphorus, parathyroid hormone, and calcium in chronic kidney disease is poor. JAMA 2011;305:1119

Insensibly one begins to twist facts to suit theories instead of theories to suit facts
Sem Dial 2011;24:22