Disturbed mineral metabolism in uremia – management

Eberhard Ritz
Heidelberg (Germany)
## Proportion of patients outside target range – *DOPPS study*

<table>
<thead>
<tr>
<th>country</th>
<th>% PTH &lt;150 pg/ml</th>
<th>% PTH &gt; 300 pg/ml</th>
<th>% Ca x P &gt; 55 mg²/dl²</th>
<th>% phosphate &gt; 5,5 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>55,6</td>
<td>21,4</td>
<td>38,0</td>
<td>45,1</td>
</tr>
<tr>
<td>Germany</td>
<td>50,5</td>
<td>25,5</td>
<td>56,5</td>
<td>69,6</td>
</tr>
<tr>
<td>Italy</td>
<td>52,6</td>
<td>25,5</td>
<td>35,1</td>
<td>37,8</td>
</tr>
<tr>
<td>Japan</td>
<td>58,5</td>
<td>19,1</td>
<td>43,1</td>
<td>53,6</td>
</tr>
<tr>
<td>Spain</td>
<td>50,8</td>
<td>27,5</td>
<td>43,2</td>
<td>46,4</td>
</tr>
<tr>
<td>England</td>
<td>47,8</td>
<td>31,2</td>
<td>44,9</td>
<td>50,8</td>
</tr>
<tr>
<td>USA</td>
<td>48,8</td>
<td>29,3</td>
<td>43,8</td>
<td>52,0</td>
</tr>
</tbody>
</table>

Vitamin D and active vitamin D
Mortality according to 25(OH)D quartiles – Ludwigshafen (LURIC) study

Frequency distribution

L = both 25(OH)D and 1,25(OH)₂D low
H = both 25(OH)D and 1,25(OH)₂D high

Mortality

L = both 25(OH)D and 1,25(OH)₂D low
H = both 25(OH)D and 1,25(OH)₂D high

Vitamin D intake and risk of type 2 diabetes
(Nurses Health Study)

Solanum malacoxylon

“entque secco”

Hypercalcemia of cattle in Argentina
Francois Lignière, 1898
Iberian rock lizard \((Lacerta monticola)\)

Martín J. and López P.,
Vitamin D supplementation increases the attractiveness of males’ scent for female Iberian rock lizards
Vitamin D in the diet increases Cholest-5,7-dien-3-ol in apocrine femoral glands of male lizards and increases their sexual attractiveness for females.

Treatment with (active) vitamin D – effects beyond mineral metabolism and bone
Injectable vitamin D and mortality according to Ca, P and PTH

Lower cardiovascular mortality in HD patients on active vitamin D therapy

Prospective observational study – inception cohort

at baseline
- low 25(OH)D$_3$
- low 1,25(OH)$_2$D$_3$

higher 1 year mortality

Thadhani R., Boston, 2006
DOPPS results – 
*iv vitamin D vs. no vitamin D*

**HR=0.80**

US-only, all patients, allows switches on/off IV Vit. D

**HR=0.86**

All DOPPS, all patients, allows switches on/off IV Vit. D

**HR=0.89**

US-only, incident patients, one-way-only switch onto IV Vit. D

Young, ASN TH-PO735 2005
Better survival of dialysis patients with Paricalcitol

![Graph showing survival rates of dialysis patients on Paricalcitol and Calcitriol. The survival rate is significantly higher for Paricalcitol patients compared to Calcitriol patients after 20 months. The difference is statistically significant (P<0.001).](Teng, New Engl J Med (2003) 349:446)
Paricalcitol as Compared with Calcitriol in Patients Undergoing Hemodialysis

Tilman B. Drüeke, M.D., and David A. McCarron, M.D.

Secondary hyperparathyroidism, a common consequence of chronic kidney disease, results from abnormal regulation of calcium and phosphate homeostasis. Three factors are central to its development of intact parathyroid hormone in patients undergoing hemodialysis who have severe forms of secondary hyperparathyroidism and also prevents its progression in patients who have less severe, earlier-
Hypertension and high renin expression in vitamin D receptor -/- mice

腹泻 vitamin D suppresses renin expression and lowers blood pressure and LVH

Cardiac hypertrophy in VDR -/- mice

Xiang, Am.J.Physiol.(2005) 288:E125
Regression of LVH by 1α-calcidol iv in HD patients

Is treatment with the precursor molecule vitamin also effective?
25-HYDROXY-VITAMIN-D IN NEPHROTIC SYNDROME

H. Schmidt-Gayk
Christa Grawunder
W. Tschöpe

W. Schmitt
E. Ritz
V. Pietsch

K. Andrassy
Medizinische Universitäts Klinik, Heidelberg, Federal Republic of Germany

R. Bouillon
Katholieke Universiteit, Rega Instituut, Leuven, Belgium

Lancet (1977) ii:105
Low 25(OH)D concentrations irrespective of seasonal adjustment

Schmitt-Gayk, Lancet (ii): 105
In proximal tubule:
uptake of complex D-binding protein/25(OH)D$_3$ via megalin


Megalin expression reduced in proteinuric conditions
megalin expression induced by 1,25(OH)$_2$D$_3$ treatment
1,25(OH)$_2$D$_3$ concentrations at different stages of CKD.

PTH – survival risk must be interpreted in the context of other abnormalities of Ca,P metabolism

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal PTH, Ca, P</td>
<td>1.0</td>
</tr>
<tr>
<td>normal PTH, Ca↑, P↑</td>
<td>↑</td>
</tr>
<tr>
<td>PTH↑, Ca↑, P↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>PTH↓, Ca↓, P↓</td>
<td>↑↑↑*</td>
</tr>
</tbody>
</table>

* the group most likely to have not received active vitamin D?

Why lack of active vitamin D? 
\[1,25(OH)_{2}D_{3}\]

- reduced uptake of 25(OH)D$_3$ by proximal tubular epithelial cells (megalin defect)$\Rightarrow$
  (substrate deficiency)
- not compensated by sufficient activation of 1-α-hydroxylase
  (inappropriate synthesis)
Strategies for vitamin D-related interventions in CKD stages 3, 4 & 5

**Strategy 1:**
Provide vitamin D₃ to maintain plasma 25-OH-D until renal enzyme can no longer sustain blood calcitriol.

**Strategy 2:**
Replace calcitriol or a vitamin D analog to restore classical & non-classical functions of vitamin D.
Progression of secondary HPT -
*progressively higher doses of vitamin D required*

Treatment with vitamin D and/or active vitamin D

- **25(OH)D deficiency** – strongly correlated to hyperparathyroidism (probably consequence of 1,25 synthesis in parathyroids)

- **New role of active vitamin D** ⇔
  better patient survival !
  pleiotropic effects ? (renin, cardiac mechanisms?)

- **Disadvantages of vitamin D therapy**
  (dose dependent. Kestenbaum):
  - positive Ca balance,
  - increase of S-phosphate concentration,
  - predisposition to vascular calcification ?

- **diminished parathyroid response** because of VDR receptor downregulation
• Vitamin D and active vitamin D
• PTH and calcium sensing
Calcium sensing receptor (CaR)

controls dimerization and normal receptor function

agonist binding
Olfactory sensing of Ca\(^{++}\) by CaSr homologue

Reaction of parathyroid to decrease of ionised Ca\(^{2+}\)
Prevention of parathyroid hyperplasia by calcimimetics

Tissue specific inhibition of proliferation of parathyroid cells

BrdU-positive cells (%)

- Sham
- NX
- 568 low
- 568 high

Parathyroid cells
Thyroid C-cells
Calcium-receptor

• expression decreased in uremia, including uremic patients with nodular hyperplasia of parathyroids,

nevertheless

• dose response relationship of calcimimetics unchanged in uremia

Calcium sensing receptor is upregulated by vitamin D, but not by calcium


1,25(OH)$_2$D$_3$ increases Ca$^{++}$ sensitivity of PTH secretion in HD patients


⇒ - increased Ca$^{++}$ sensitivity of parathyroid
- reduced active intestinal Ca transport
argument for calcimimetic plus active vitamin D ?
Cinacalcet for Secondary Hyperparathyroidism in Patients Receiving Hemodialysis

Cinacalcet decreases PTH concentration

Cinacalcet reduces Ca x P product

![Graph showing the reduction of calcium-phosphorus product with Cinacalcet compared to Placebo over weeks. The graph indicates a significant reduction with Cinacalcet, as indicated by the statistical significance (P<0.001).](image)

No. of Patients

<table>
<thead>
<tr>
<th></th>
<th>Cinacalcet</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>371 354 335 330 314 308 294 302 294 281 275 270 258 250</td>
<td>370 354 338 344 333 322 322 315 308 304 295 290 288 286</td>
</tr>
</tbody>
</table>

SNX rats on calcimimetic or after PTX – less glomerular and tubulointerstitial cell proliferation

Progression of secondary HPT -

⇒ progressively higher doses of vitamin D required
(decrease of vitamin D and calcium sensing receptors)

Tominaga, Curr Opin Nephrol Hypertens (1996)5:336
if PTH > 50 pmol/L ( ~ 500 pg/ml )
despite treatment with active vitamin D
or
if treatment contraindicated because of hypercalcemia / hyperphosphatemia

→ in the past: consider parathyroidectomy

→ new consideration: Cinacalcet?
Rationale for parathyroidectomy

- nodular parathyroid hyperplasia,
- monoclonal growth and chromosomal abnormalities,
- loss of tumor suppressor genes,
- downregulation of vitamin D receptor,
- unresponsiveness to active vitamin D
Less longterm mortality after PTX in hemodialysed patients

Risk lower by 15% after PTX

Survival of HD patients after PTX

Guidance for Evaluating Elevated PTH Levels

• Is it due to excess PTH secretion?
  – regulated by calcium via CaSR
  – hypocalcemia
• Is it due to excess PTH gene transcription?
  – regulated by vitamin D
  – regulated by calcium
  – serum calcitriol \((1,25(OH)_2D)\) levels
  – vitamin D nutrition \((25(OH)D)\)
  – serum calcium concentration
• Is it due to refractory parathyroid gland enlargement from nodular hyperplasia?
  – regulated by calcium via CaSR
  – triggered by phosphorus via TNFα and p21
• Vitamin D and active Vitamin D
• PTH and calcium sensing
• Phosphate control
Periarticular calcification
Both high and low turnover bone disease favour calcification

Ca^{++} PO_4^{3+} calcification

net Ca release

failure to take up Ca
Calcification active process: vascular smooth muscle cells into osteoblast-like cells

Giachelli, Am J Kidney Dis (2001);38: S34
Calcification
Promotors ↔ Inhibitors

Promotors
• ↑ phosphate, ↑ calcium
• ↑ Ca x P product
• ↑ vitamin D
• “uremic milieu”
• inflammation

Inhibitors
• systemic, e.g..
  • fetuin-A
• local, e.g..
  • matrix Gla protein
  • osteoprotegerin
Serum P increases concentration dependently cardiovascular risk in individuals without renal disease –
(Framingham study)


3368 offspring mean age: 44 years follow-up: 16 years
Relation between serum phosphate and all cause mortality in nonrenal patients  
*(CARE-study)*

<table>
<thead>
<tr>
<th>All-cause death</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt; 2.5$ mg/dL</td>
<td>9 (6.9)</td>
<td>0.78</td>
<td>0.40–1.52</td>
</tr>
<tr>
<td>$2.5–3.4$ mg/dL</td>
<td>229 (8.7)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>$3.5–3.9$ mg/dL</td>
<td>104 (10.0)</td>
<td>1.25</td>
<td>0.98–1.58</td>
</tr>
<tr>
<td>$\geq 4.0$ mg/dL</td>
<td>33 (10.3)</td>
<td>1.42</td>
<td>0.97–2.07</td>
</tr>
<tr>
<td>Per 1 mg/dL</td>
<td>1.27</td>
<td>1.02–1.58</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Tonelli, Circulation (2005)112:2627*
Adjusted outcomes as a function of S-phosphate in nonrenal patients

causes of death

Tonelli, Circulation (2005)112:2627
Hyperphosphataemia—a silent killer of patients with renal failure?

Kerstin Amann¹, Marie-Luise Gross¹, Gérard M. London³ and Eberhard Ritz²

¹Department of Pathology and ²Department of Internal Medicine, Ruperto Carola University, Heidelberg, Germany and ³Hôpital Manhes, Fleury Mérogis, France
PTH mRNA –
stabilised by high P via greater availability of cytoplasmic protein AUF for binding to nontranslated 3’region

Yalcindag, JASN (1999) 10: 2562
Serum phosphate and mortality in dialysed patients

<table>
<thead>
<tr>
<th>Serum Phosphate (mmol/L)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.36-1.45</td>
<td>1.00</td>
</tr>
<tr>
<td>1.49-1.78</td>
<td>1.00</td>
</tr>
<tr>
<td>1.81-2.10</td>
<td>1.02</td>
</tr>
<tr>
<td>2.13-2.52</td>
<td>1.18*</td>
</tr>
<tr>
<td>2.55-5.46</td>
<td>1.39**</td>
</tr>
</tbody>
</table>

- *p < 0.05
- **p < 0.01

Causes of death in hemodialysed patients

$\text{PO}_4 > 6.5 \text{mg/dL}$ vs $2.4-6.5 \text{mg/dL}$

<table>
<thead>
<tr>
<th>Cause</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>1.41***</td>
</tr>
<tr>
<td>Sudden death</td>
<td>1.20**</td>
</tr>
<tr>
<td>Other cardiac</td>
<td>1.18</td>
</tr>
<tr>
<td>CVA</td>
<td>1.26</td>
</tr>
<tr>
<td>Infect.</td>
<td>1.20*</td>
</tr>
<tr>
<td>Other Known</td>
<td>1.07</td>
</tr>
<tr>
<td>Unknown Known</td>
<td>1.25*</td>
</tr>
<tr>
<td>Missing death</td>
<td>1.27</td>
</tr>
</tbody>
</table>

Serum phosphate and survival in predialysis patients with renal failure

after adjustment; serum phosphate > 3.5 mg/dl significantly increased risk of death

Coronary plaques in dialysed patients – more severe calcification

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>No Renal Disease (n=27)</th>
<th>Endstage Renal Disease (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type III</td>
<td>Preatheroma</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Type IV</td>
<td>Atheroma</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Type V</td>
<td>Fibroatheroma</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Type VI</td>
<td>Complicated Plaque</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Type VII</td>
<td>Calcified Plaque</td>
<td>5</td>
<td>18</td>
</tr>
</tbody>
</table>

Schwarz, NDT (2000) 15: 218
Oh, Circulation (2002) 106: 100
Coronary calcium score (CACS) – predictor of survival in HD - patients

Matsuoka (2004), Clin Exp Nephrol 8: 54
“My bones are getting softer, but my arteries are getting harder so it balances out.”
High serum calcium and/or phosphorus ➔ vascular calcification

Calcification of aortic media and intima increases mortality in dialysis patients

London, Nephrol Dial Transplant 2003;18:1731
Hyperphosphatemia control –

1. lowering of dietary phosphate intake

High phosphate of cow milk

- growth velocity (and P requirement)
  calf > baby
- in (premature) babies: unmodified cow milk
  → hypocalcemia

Phosphate content of common food items

(mg P per 100 g of food)

sausages →
addition of phosphate
(hygroscopic!)

Cupisti,
J NEPHROL 2003; 16: 29
Hyperphosphatemia control –

2. removal of P by dialysis

- Increase the length of the dialysis session
  
  Charra, Kidney Int (1992) 41: 1286

- Increase the frequency of the dialysis sessions
  – daily dialysis

  Buoncristiani, Kidney Int 1988; 33 (Suppl 24): s137

- nocturnal haemodialysis (even hypophosphatemia !)

Limitation –
Time course of serum phosphate concentration during and after one HD session

Serum Phosphate Levels
% of Predialysis Value

Why is removal of phosphate by conventional dialysis so unsatisfactory?
What are alternative (or complementary) strategies?

- $P$ dialysable, but slow equilibration between intra- / extra-cellular pool
- relatively limited removal by high efficiency dialysis
- extremely effective removal by long, slow dialysis (hypophosphatemia !)

$\Rightarrow$ removal by conventional dialysis not sufficient, $P$ binders required

Hyperphosphatemia control –

3. inhibition of intestinal binding or transport of P

- Aluminium salts
- Ca carbonate
- Sevelamer (Renagel®)
- Lanthanum carbonate (Fosrenol®)
- Nicotinamide
- [Cinacalcet (Mimpara®)]
“If a lot of cures are suggested for a disease it usually indicates that the disease is uncurable.”

Cherry Orchard, Tschechow
Changes of serum-P in hemodialysed patients ingesting nicotinamide (inhibition of active intestinal transport)

Hyperphosphatemia control

Sevelamer

- Not absorbed in the GI tract

- Does not interfere with absorption of other drugs
Less increase of coronary calcification with Sevelamer than with Ca-carbonate

<table>
<thead>
<tr>
<th></th>
<th>Sevelamer (n=23)</th>
<th>Calcium Carbonate (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agatston score baseline</strong></td>
<td>1488 ± 1820</td>
<td>1259 ± 1848</td>
</tr>
<tr>
<td><strong>Increase within 2 years</strong></td>
<td>142 ± 829</td>
<td>637 ± 898</td>
</tr>
<tr>
<td>Median + 20</td>
<td>Median + 83</td>
<td></td>
</tr>
</tbody>
</table>

Sevelamer and cardiac endpoints – is it phosphate lowering or lipid lowering?

*I don’t care what colour the cat is – so long as it catches mice*

*Deng Hsiao Ping*

*1904-1997*
Lanthanum-based oral binders -
HD patients, randomized, double-blind placebo-controlled study

Predosing
Titration
Randomized treatment

Serum phosphate (mg/dl)

Vis1 Vis2 1 2 3 4 5 6 7 8 9 10
weeks

lanthanum N=49
placebo N=44

P<0.0001

Lanthanum-based oral binders

Multicentre clinical study

- 98 patients
  - 49 lanthanum carbonate up to 3750 mg/day (mean dose 1250)
  - 49 calcium carbonate up to 9000 mg/day (mean dose 2000)

- well tolerated
- comparable side effects (53% vs 47%)
- lower incidence of hypercalcemia
- comparable phosphataemia control
- no aluminium-like toxic effects on the bone

Hyperphosphatemia control -
Lanthanum-based oral binders

- The long-term safety of lanthanum agents in humans needs to be accurately monitored in further phase III studies and throughout the post-marketing period

Locatelli, Drugs (2003) 6: 688
• Vitamin D and active Vitamin D
• PTH and calcium sensing
• Phosphate control
• Calcium balance and dialysate calcium
• Outlook
Ca-carbonate vs Sevelamer – 
more hypoparathyroidism, more bone loss

TREAT-TO-GOAL
6.5g Sevelamer vs 3.9g Ca carbonate
Ca carbonate: PTH ↓ 200 → 138 pg/ml
   thoracic vertebral bone ↓

Ca carbonate: PTH ↓
   more hypercalcemic episodes
   loss of trabecular bone density

• **Dialysate Calcium concentration**

  avoid 1.75 mmol/L
  
  1.5 mmol/L
  
  1.25 mmol/L in adynamic bone disease
  
  - *ionized Ca**⁺⁺* ↓
  
  - *hypercalcemia episodes* ↓
  
  - *increase in PTH (4-fold)*
  
  - *bone specific AP* ↑


• **Calcium per os**

  K-DOQI guidelines

  *dietary calcium and calcium containing P-binders* < 2000 mg/day
Genesis of secondary hyperparathyroidism

the classical trio

• $Ca^{++} \downarrow$
• $P \uparrow$
• *active vitamin D* $\downarrow$

now a quartet?

• $Ca^{++} \downarrow$
• $P \uparrow$
• *active vitamin D* $\downarrow$
• $FGF23 \uparrow$

⇨ *we have to rewrite the textbooks and probably face new interventions*
Thank you for your attention
Changes of 25(OH)D concentrations throughout the year according to monthly quartiles

Ludwigshafen (LURIC) study, coronary patients