Kidney Bone Disease
What happens when the kidney fails?

- Progression of kidney damage >> mineral metabolism
  - Bone histology in ESRF
  - Concept of calcium loading in CKD
  - Non-calcium containing phosphate binders
  - Lanthanum: a safe phosphate binder?
  - Lanthanum and the calcium loading concept

M.E. De Broe
Stockholm
31 March 2009
Consequences of phosphate accumulation in chronic renal failure

High phosphate levels due to the phosphate accumulation in renal failure (1) increase the PTH secretion by the parathyroid glands (2). The resulting increase in osteoclast activity will raise the phosphate levels further (3). Renal failure itself, together with increased serum phosphate levels, leads to a decrease in 1α-hydroxylase activity (4), resulting in reduced 1,25-(OH)2 vitamin D3 levels (5).
*In vitro* effect of increasing phosphate concentration on free calcium

**Ferrari P et al, Kidney Int 2007**

- pH 7.4
- Fixed total calcium 2.6 mmol/L
- Stronger effect of phosphate at low compared to normal albumin concentrations

Normal Ps=1.8 mmol/l
Distribution of Serum Phosphorus

From the U.S. Renal Data System: Case Mix Adequacy Study (CMAS) and Dialysis Morbidity and Mortality Study (DMMS)

Hyperphosphatemia ≈ ↑ morbidity

Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: 
Results of the study to evaluate early kidney disease

PTH secretion, PTH gene expression, parathyroid gland hyperplasia

1. CASR cell surface G protein–coupled receptor extrac. Ca++
2. Vitamin D receptor nuclear receptor controlling gene transcription
3. Uncharacterized phosphate sensor
4. FGF23 is a negative regulator of parathyroid function

Quarles LD: Kidney Int 68 (S96): S24-S28, 2005
Importance of ionized calcium dependent signaling

Vitamin D dependent pathways play a 2ndary role

<table>
<thead>
<tr>
<th></th>
<th>VDR –/- (Vit D deficiency)</th>
<th>1αOHase –/-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcemia</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Phosphatemia</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>PTH</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Osteomalacia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gland hyperplasia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>↑↑</td>
<td>↓↓undetectable</td>
</tr>
</tbody>
</table>

Feeding 2% calcium normalizes everything; signaling through CaSR is sufficient to prevent SHPT and gland hyperplasia in tissues incapable to respond to Vit D

Calcitriol normalizes everything; Ca administration almost everything
1. CASR cell surface G protein–coupled receptor extrac. Ca++
2. Vitamin D receptor nuclear receptor controlling gene transcription
3. Uncharacterized phosphate sensor
4. FGF23 is a negative regulator of parathyroid function

Quarles LD: Kidney Int 68 (S96): S24-S28, 2005
Fibroblast growth factor 23

- **BOWEL**: reduces Ca & Pi absorption in small bowel
- **FGF-23** possibly inhibits mineralization and release from osteocytes/osteoblasts
- **BONE**: release from osteocytes/osteoblasts
- **PARATHYROID**: negative regulator of parathyroid function
- **KIDNEY**: increases phosphaturia
- **VITAMIN D**: 1α(OH)D3 inhibits 1,25(OH)2D3
- **Klotho**: powerful

---

**Diagram Details**:
- Arrows indicate regulatory relationships:
  - FGF-23 affects BOWEL and PARATHYROID.
  - BONE release affects FGF-23.
  - VITAMIN D affects 1α(OH)D3 and 1,25(OH)2D3.
  - **Ki1** negatively affects FGF-23.
  - **Ki2** increases phosphaturia.

---

**Note**: The diagram illustrates the complex interactions between FGF-23 and other biological systems, emphasizing the regulation of mineral metabolism and vitamin D activity.
FGF 23

- FGF 23 early incr. --- normalization Ps

- Vitamin D Levels decrease --- FGF 23 excess --- renal mass?

- Posttransplant - hypoP - PTH incr.
  - 1,25 VitD decrease
  - high FGF23

- FGF23 early incr in CKD - marker of disorder
  - of P metabolism
FGF-23 predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease study

Kaplan-Meier curves of renal end points in patients with below and above optimal cutoff of plasma c-terminal (A) FGF23 concentrations and for intact (B) FGF23 concentrations below and above the median.

FGF 23 and Clinical Nephrology

- Dose dependent increase risk of death in HD patients
- FGF 23 may be a superior marker for disorders of P metabolism related CVD in CKD
- FGF23 as biomarker of CKD progression
- Phosphate binding decrease FGF 23 levels

NEJM 359, 584, 2008
JASN 18, 2600, 2007
Kidn Intern 69, 531, 2006
Atheros. 2009
PTH secretion, PTH gene expression, parathyroid gland hyperplasia

1. CASR cell surface G protein–coupled receptor extrac. Ca++
2. Vitamin D receptor nuclear receptor controlling gene transcription
3. Uncharacterized phosphate sensor
4. FGF23 is a negative regulator of parathyroid function

Quarles LD: Kidney Int 68 (S96): S24-S28, 2005
Calcimimetic agents and secondary hyperparathyroidism

AMG 073 increases CaR sensitivity to Ca^{2+}

- Parathyroid Cell
- Extracellular
- Intracellular

Activation of Second Messengers
- within minutes to hours ↔ Vit D

- PTH Synthesis and Secretion
  - In the absence of ↑ in extracellular calcium

- Serum calcium ↓
- Renal calcium excretion ↑
Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis


**Variable**

- **Overall**
  - 7.3 (4.8–11.3)

- **Sex**
  - Female: 8.8 (4.1–19.6)
  - Male: 6.0 (3.7–9.8)

- **Race**
  - White: 6.2 (3.7–103)
  - Black: 7.3 (3.4–15.6)

- **Age**
  - <65 yr: 7.0 (4.2–11.5)
  - ≥65 yr: 6.3 (3.2–12.3)

- **Duration of dialysis**
  - <1 yr: 2.4 (1.4–7.2)
  - 1–5 yr: 9.9 (5.3–18.7)
  - >5 yr: 1.7 (2.0–6.8)

- **Parathyroid hormone level**
  - 300–500 pg/ml: 6.1 (3.8–9.7)
  - 501–800 pg/ml: 20.1 (6.5–61.4)
  - >800 pg/ml: 9.3 (1.2–70.1)

- **Calcium level**
  - ≤10.2 mg/dl: 6.5 (4.1–16.2)
  - >10.2 mg/dl: 9.4 (3.3–15.5)

- **Phosphorus level**
  - ≤6.0 mg/dl: 6.4 (3.8–10.8)
  - >6.0 mg/dl: 7.1 (1.3–13.9)

- **Calcium–phosphorus product**
  - ≤60 mg^2/dl^2: 5.9 (3.6–9.6)
  - >60 mg^2/dl^2: 13.6 (5.9–31.4)

- **Diabetes**
  - Yes: 6.4 (3.3–12.3)
  - No: 6.9 (4.1–11.8)

- **Vitamin D sterol use**
  - Yes: 6.2 (4.1–9.6)
  - No: 6.8 (2.1–22.8)
Achieving NKF/DOQI™ bone metabolism and disease treatment goals with cinacalcet HCl

Long-term treatment of secondary hyperparathyroidism with the calcimimetic cinacalcet HCl

Table 3. The proportion of patients who achieved the NKF-K/DOQI™ targets

<table>
<thead>
<tr>
<th>Recommended NKF-K/DOQI™ targets</th>
<th>Baseline of qualifying study n (%)</th>
<th>Week 52 n (%)</th>
<th>Week 100 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH ≤300 pg/ml</td>
<td>6 (10%)</td>
<td>30 (52%)a</td>
<td>35 (59%)a</td>
</tr>
<tr>
<td>Serum calcium ≥8.4 to ≤9.5 mg/dl</td>
<td>25 (42%)</td>
<td>23 (40%)</td>
<td>22 (37%)</td>
</tr>
<tr>
<td>Serum phosphorus ≥3.5 to ≤5.5 mg/dl</td>
<td>19 (32%)</td>
<td>21 (37%)</td>
<td>22 (37%)</td>
</tr>
<tr>
<td>Ca×P &lt;55 mg²/dl²</td>
<td>25 (42%)</td>
<td>32 (56%)</td>
<td>31 (53%)</td>
</tr>
</tbody>
</table>

Moe SM et al: Nephrol Dial Transplant 20, 2186-2193, 2005
Calcimimetics – Secondary hyperparathyroidism

- Bioavailability is low
- Metabolism is variable – pharmacokinetics?
- Long term use
- Hypocalcemia – calcium load? uptake in bone?
  5%: < 7.5 mg%
- Phosphate handling – dialysis – stage 3 - 4 CKD
  hyperphosphatemia, hypocalcemia, hypercalciuria
- Effects on bone – vascular calcification
- Effects on other systems – calciuria
- up and down ↔ persistent effect of PTH
Kidney Bone Disease
What happens when the kidney fails?

✓ Progression of kidney damage >> mineral metabolism

➤ Bone histology in ESRF

- Concept of calcium loading in CKD
- Non-calcium containing phosphate binders
- Lanthanum: a safe phosphate binder?
- Lanthanum and the calcium loading concept
Classification of renal osteodystrophy

- Normal bone
- Adynamic bone
- Osteomalacia
- Mixed lesion

<table>
<thead>
<tr>
<th>Classification</th>
<th>Bone Formation Rate (µm²/mm²/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Osteomalacia</td>
<td>97</td>
</tr>
<tr>
<td>Adynamic</td>
<td>12</td>
</tr>
<tr>
<td>Mixed lesion</td>
<td>613</td>
</tr>
<tr>
<td>Osteitis fibrosa*</td>
<td></td>
</tr>
<tr>
<td>Mild lesion*</td>
<td></td>
</tr>
</tbody>
</table>

*: both classified as hyperparathyroidism
:with fibrosis
## Summary of published prevalences (%) of different types of ROD over the years in dialysis patients

<table>
<thead>
<tr>
<th>Reference (et al)</th>
<th>Type of patients</th>
<th>N</th>
<th>Index of Al presence</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ABD</td>
</tr>
<tr>
<td>Sherrard, 1972</td>
<td>HD</td>
<td>67</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Liach, 1986</td>
<td>HD</td>
<td>142</td>
<td>Major. of OM &amp; ABD</td>
<td>7%</td>
</tr>
<tr>
<td>Salusky, 1988</td>
<td>CAPD (children)</td>
<td>44</td>
<td>23%</td>
<td>11%</td>
</tr>
<tr>
<td>Moriniere, 1989</td>
<td>HD</td>
<td>42</td>
<td>9.5%</td>
<td>24%</td>
</tr>
<tr>
<td>Maluche, 1992</td>
<td>HD+CAPD</td>
<td>1803</td>
<td>56.4% 62.2%</td>
<td>5%</td>
</tr>
<tr>
<td>Sherrard, 1993</td>
<td>HD</td>
<td>117</td>
<td>15%</td>
<td>36%</td>
</tr>
<tr>
<td>Sherrard, 1993</td>
<td>CAPD</td>
<td>142</td>
<td>25%</td>
<td>36%</td>
</tr>
<tr>
<td>Torres, 1995</td>
<td>HD</td>
<td>49</td>
<td>32%</td>
<td>12%</td>
</tr>
<tr>
<td>Torres, 1995</td>
<td>CAPD</td>
<td>32</td>
<td>48%</td>
<td>10%</td>
</tr>
<tr>
<td>Couttenye, 1996</td>
<td>HD</td>
<td>103</td>
<td>5%</td>
<td>37%</td>
</tr>
<tr>
<td>Coen, 1998</td>
<td>HD</td>
<td>41</td>
<td>0%</td>
<td>11%</td>
</tr>
<tr>
<td>Canavese, 1998</td>
<td>HD</td>
<td>80</td>
<td>35%</td>
<td>9%</td>
</tr>
<tr>
<td>Sanchez, 2000</td>
<td>CAPD</td>
<td>57</td>
<td>14%</td>
<td>63%</td>
</tr>
<tr>
<td>Gerakis, 2000</td>
<td>HD</td>
<td>62</td>
<td>34%</td>
<td>23%</td>
</tr>
<tr>
<td>Changsirikulchai, 2001</td>
<td>HD</td>
<td>39</td>
<td>3.5%</td>
<td>41%</td>
</tr>
<tr>
<td>Changsirikulchai, 2001</td>
<td>CAPD</td>
<td>17</td>
<td></td>
<td>41%</td>
</tr>
<tr>
<td>Ballanti, 2001</td>
<td>HD</td>
<td>37</td>
<td>0%</td>
<td>14%</td>
</tr>
</tbody>
</table>

GS Spasovski, PhD thesis, University of Skopje, Macedonia, 2002
### Summary of published prevalences (%) of different types of ROD over the years in patients with chronic renal failure not yet in dialysis

<table>
<thead>
<tr>
<th>Reference (et al)</th>
<th>Type of patients</th>
<th>N</th>
<th>Index of Al presence</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ABD</td>
</tr>
<tr>
<td>Eastwood, 1982</td>
<td>CRF</td>
<td>38</td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>Mora Palma, 1983</td>
<td>ESRD</td>
<td>327</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Dahl, 1988</td>
<td>ESRD</td>
<td>60</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Hutchison, 1988</td>
<td>ESRD</td>
<td>34</td>
<td>ND</td>
<td>16%</td>
</tr>
<tr>
<td>Cohen-Solal, 1992</td>
<td>ESRD</td>
<td>27</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Hutchison, 1993</td>
<td>ESRD</td>
<td>30</td>
<td>6.6%</td>
<td>27%</td>
</tr>
<tr>
<td>Hernandez, 1994</td>
<td>ESRD</td>
<td>92</td>
<td>4.3%</td>
<td>33%</td>
</tr>
<tr>
<td>Torres, 1995</td>
<td>ESRD</td>
<td>38</td>
<td>3.4%</td>
<td>48%</td>
</tr>
<tr>
<td>Hamdy, 1995</td>
<td>CRF</td>
<td>176</td>
<td>2%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Coen, 1996</td>
<td>CRF</td>
<td>76</td>
<td>0%</td>
<td>12%</td>
</tr>
<tr>
<td>Shin, 1999</td>
<td>ESRD</td>
<td>58</td>
<td>0%</td>
<td>24%</td>
</tr>
<tr>
<td>Ballanti, 2001</td>
<td>ESRD</td>
<td>27</td>
<td>0%</td>
<td>22%</td>
</tr>
</tbody>
</table>

*GS Spasovski, PhD thesis, University of Skopje, Macedonia, 2002*
Bone biopsy study in Macedonia

- Prospective unselected bone biopsy study of all pre-dialysis patients over 9 months
- ROD histology

 approximate area: 25000 km²
2 million inhabitants

Diagnosis of adynamic bone disease in hemodialysis patients

BAP \( \leq 27 \text{ U/L} \)

OC \( \leq 14 \text{ ng/ml} \)

iPTH \( \leq 150 \text{ pg/ml} \)

OC: Osteocalcin
BAP: Bone alkaline phosphatase
Predictive values of biochemical markers of adynamic bone in hemodialysis patients

Couttenye et al, NDT 1996
Kidney Bone Disease
What happens when the kidney fails?

- Progression of kidney damage >> mineral metabolism
- Bone histology in ESRF
- Concept of calcium loading in CKD
  - Non-calcium containing phosphate binders
  - Lanthanum: a safe phosphate binder?
  - Lanthanum and the calcium loading concept
CALCIUM LOAD in END STAGE RENAL FAILURE PATIENTS

- No renal function
- Administration of Vitamin D
- Use of Calcium containing Phosphate binders (8 – 15 mEq/dialysis day)
- Use of non-calcium containing Phosphate binders
- Calcium load through dialysate
  - peritoneal dialysis (2.5 – 3.0 mEq/l / serum iCa 1.8 - 2.5 mEq/l)
CALCIUM LOAD in END STAGE RENAL FAILURE PATIENTS

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- Use of non calcium containing Phosphate binders
- Calcium load through dialysate
  - peritoneal dialysis (2.5 – 3.0 mEq/l / serum iCa 1.8- 2.5 mEq/l)
- Diet
Calcium absorption across epithelia

Mechanism of epithelial Ca\(^{2+}\) transport
CALCIUM LOAD in END STAGE RENAL FAILURE PATIENTS

• No renal function

• Administration of Vitamin D

• Use of Calcium containing Phosphate binders (8 – 15 mEq/day)

• Use of non calcium containing Phosphate binders

• Calcium load through dialysate

• peritoneal dialysis (2.5 – 3.0 mEq/l / serum iCa 1.8- 2.5 mEq/l)
Effect of phosphate binder

- Bone Demineralization
- Osteomalacia

Phosphate binder

GI intake 1400 mg/d

Absorption of Ca ↑↑

Excretion of P ↑↑

Stool 490 mg/d

Digestive juice phosphorus

Formation 210 mg/d

Serum Phosphorus (Pi) ↓
2-4.5 mg/dl
0.65-1.4 mmol/L

Urinary P ↓↓
Urinary Ca ↓↓

DIALYSIS PATIENT


Effect of manipulating serum phosphorus with phosphate binder on circulating PTH and FGF23 in renal failure rats


Effects of (a) continuous and (b) intermittent treatment with sevelamer on serum phosphorus (left) and calcium (right) levels.
Aluminum gels in the management of renal phosphatic calculi

CALCIUM LOAD in END STAGE RENAL FAILURE PATIENTS

- No renal function

- Administration of Vitamin D

- Use of Calcium containing Phosphate binders (8 – 15 mEq/day)

- Use of non calcium containing Phosphate binders

- Calcium load through dialysate

- peritoneal dialysis (2.5 – 3.0 mEq/l / serum iCa 1.8- 2.5 mEq/l)
Calcium in blood, normal value: 2.2-2.7 mmol/l
4.5-5 meq/L
9.0-10.5 mg/l

- Ionized or free calcium: 48%
- Calcium bound to albumin: 40%
- Calcium bound to various anions
  - phosphate
  - lactate
  - citrate
  - bicarbonate: 12%
- Ionized Calcium to be determined within 2hrs or 6hrs if stored at 4°C
Inverse relationship between ionized calcium and phosphate at all pH levels, counter ion effect.
Adynamic Bone Disease

- Decreased BFR
- Relative hypoparathyroidism
- VDR polymorphism
- VDR expression
  - Downregulation osteoblastic PTH receptor
  - Diabetes
  - Older age
  - Male gender
  - Uremic toxins
  - Growth factors
  - Al\(\uparrow\) + Fe\(\downarrow\)
  - Vit.D treatment

Ca receptor expression
- Extracellular Ca\(^{++}\)↑
- Ca loading (CaCO\(_3\)/peritoneal dialysis)

- Al\(\uparrow\) + Fe\(\downarrow\)
- Mg\(^{++}\)
- Better Pi control
- Diabetes
- Age
- Malnourishment
- Vit.D treatment
- VDR expression
Increased Skeletal Resistance to PTH in Uremia

PTH action on normal bone

Osteitis Fibrosa

Adynamic Bone

PTH action on uremic bone

From M. Fukagawa, Kobe, Japan
Arterial calcifications and bone histomorphometry in ESRD

Therapeutic interventions associated with excessive lowering of parathyroid activity (parathyroidectomy, excessive calcium or aluminum load) favor lower bone turnover and adynamic bone disease, which could influence the development and progression of arterial calcification.

Arterial media calcification in ESRD: impact on all-cause and cardiovascular mortality

NC  no calcification  
AMC  Arterial media calcification  
AIC  Arterial intima calcification

Matched for duration of HD  
Free of common carotid artery calcified plaques

Both Forms of Osteodystrophy in CKD Contribute to Hyperphosphatemia

Low Turnover Osteodystrophy

PTH

Calcium

Phosphorus

Deposition into tissues

Low Turnover Osteodystrophy

Calcium

Phosphorus

High Turnover Osteodystrophy

PTH

Vascular Calcification/Stiffness
CALCIUM LOAD in DIALYSIS PATIENTS

- Increase in serum calcium –ionized calcium
- Decrease in PTH secretion, relative hypoparathyroidism
- Low bone turn over
- Less incorporation of calcium in bone
- Higher risk for development of vascular calcifications

EFFICIENT PHOSPHATE BINDING

AVOID EXCESIVE CALCIUM LOAD
Kidney Bone Disease
What happens when the kidney fails?

- Progression of kidney damage >> mineral metabolism
- Bone histology in ESRF
- Concept of calcium loading in CKD

> Non-calcium containing phosphate binders
  - Lanthanum: a safe phosphate binder?
  - Lanthanum and the calcium loading concept
Serum Phosphorus and Mortality Risk in CKD Patients on Dialysis

![Bar chart showing relative risk of death associated with serum phosphorus concentration.](chart.png)

$n=40,538$
Fresenius Medical Care North America database

Serum Phosphorus and Mortality Risk in CKD Patients Not on Dialysis

Adjusted Hazard Ratio for Mortality

\[ \text{Adjusted for baseline age, sex, race, cerebrovascular disease, diabetes, ischemic heart disease, HF, acute renal failure, calcium intake from medications, serum calcium, inverse of baseline creatinine, time-averaged creatinine, slope of creatinine, maximal creatinine concentration, hemoglobin. CKD (CrCl 50.4 – 39.6 mL/min)} \]


n=6,730

5%

88%

7%

1.00

1.15

1.32

1.34

1.83

1.90

< 2.5

2.5-3.49

3.5-3.99

4.0-4.49

4.5-4.99

> 5.0

Serum Phosphorus (mg/dL)
<table>
<thead>
<tr>
<th>Année</th>
<th>Produit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1966</td>
<td>Carbonate de calcium</td>
</tr>
<tr>
<td>1972</td>
<td>Hydroxyde d’alumine (1976 encéphalopathie)</td>
</tr>
<tr>
<td>1986</td>
<td>Carbonate de magnésium</td>
</tr>
<tr>
<td>1986</td>
<td>Alginate de calcium</td>
</tr>
<tr>
<td>1989</td>
<td>Acétate de calcium</td>
</tr>
<tr>
<td>1995</td>
<td>Chlorure de zirconyl</td>
</tr>
<tr>
<td>1996</td>
<td>Kétoglutarate de calcium</td>
</tr>
<tr>
<td>1999</td>
<td>Sulfate de fer hydrolysé</td>
</tr>
<tr>
<td>2000</td>
<td>Sevelamer</td>
</tr>
<tr>
<td>2001</td>
<td>Carbonate de lanthane</td>
</tr>
<tr>
<td>2003</td>
<td>Inhibiteurs du transport intest. du phosphate</td>
</tr>
</tbody>
</table>
Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients

### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sevelamer (N = 99)</th>
<th>Calcium (N = 101)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years (mean ± SD)</td>
<td>57 ± 14</td>
<td>56 ± 16</td>
<td>0.88</td>
</tr>
<tr>
<td>Sex % female</td>
<td>36%</td>
<td>34%</td>
<td>0.77</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>17%</td>
<td>23%</td>
<td>0.34</td>
</tr>
<tr>
<td>White</td>
<td>71%</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>12%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Diabetes %</td>
<td>32%</td>
<td>33%</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension %</td>
<td>86%</td>
<td>83%</td>
<td>0.70</td>
</tr>
<tr>
<td>Smoker %</td>
<td>3%</td>
<td>8%</td>
<td>0.21</td>
</tr>
<tr>
<td>Primary Cause of ESRD %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>16%</td>
<td>17%</td>
<td>0.66</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>26%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Diabetics</td>
<td>23%</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>9%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>26%</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Dialysis vintage years, median</td>
<td>3.6</td>
<td>2.9</td>
<td>0.24</td>
</tr>
<tr>
<td>Phosphate binder use prior to study entry %</td>
<td></td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>38%</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>Calcium acetate</td>
<td>33%</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>Calcium + aluminum</td>
<td>14%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Sevelamer</td>
<td>3%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Other combinations</td>
<td>12%</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>

Compared with calcium-based phosphate binders, sevelamer is less likely to cause hypercalcemia, low levels of PTH, and progressive coronary and aortic calcification in hemodialysis patients.

Change in calcification scores from baseline to weeks 26 and 52 in pt with score>30 at baseline.
Lanthanum: the element

- MW: 139 Da (2 stable isotopes)
- Silvery white, malleable, ductile rare earth element; occurring at varying concentrations in terrestrial crust and surface water.

**Tri-valent hard acid cation → high affinity for phosphate**

\[ \text{Ks} = [\text{La}^{3+}][\text{PO}_4^{3-}] = 7.08 \times 10^{-27} \]

= solubility constant
Patient Exposure to Fosrenol®

- Extensively studied phosphate binder at launch
  - Over 5500 patients with clinical evaluation

- Market experience in the USA since January 2005 and in the EU since 2006
  - Over 100,000 patients treated

- Through extended treatment, some 28 patients have now received Fosrenol® for 5 years or more, 22 on 6th year of treatment.

Shire data on file
Efficacy of Fosrenol® versus placebo

Adapted from: Joy MS, Finn WF. *Am J Kidney Dis* 2003;42:96–107

*1.0 mmol/L = 3.1 mg/dL*

*P < 0.0001 between treatment groups at endpoint*
Efficacy of Fosrenol®: long term

1.0 mmol/L = 3.1 mg/dL

Adapted from Hutchison A et al. Poster presented at ASN 2005
High phosphate-binding affinity *in vitro*: independent of pH

Lanthanum carbonate binds phosphate across a wide pH range

Similar affinity to aluminium hydroxide

Adapted from: Damment SJP, Webster I. Poster presented at ASN 2003
Selective phosphate binding: no displacement by bile acids

Adapted from: Autissier V et al. Poster presented at ASN 2005
Summary of randomised studies

Overall, randomised studies (USA, Europe, Taiwan) confirm that:

- Lanthanum carbonate is a consistently effective binder of dietary phosphate
- Doses up to 3000 mg/day reduce serum phosphate to target levels in the majority of patients
- Maintenance of target phosphate levels is similar between lanthanum carbonate and standard therapy
- Phosphate levels are controlled in long-term use (up to 154 weeks of treatment)

Hutchison AJ. Nephron Clin Pract 100: c8–19, 2005
Ultrastructural localisation of aluminum

- Parathyroid
- Liver
- Bone

**Microscopic**

- Secretory granules
- Lysosomes
- Aluminon® staining
- Perl's staining

**LAMMA**

- Mineralisation front
Faecal excretion

Metabolism of two trivalent cations: Aluminum - Lanthanum

Aluminum

- Significant aluminum intake through breathing and food
- Marginal lanthanum intake through breathing and food
- Gastro-int. abs. of Al decreased by citrate, PTH, uremic state, ...
- Gastro-int. abs. of Al increased by citrate, PTH, uremic state, ...
- Faecal excretion of Al-contaminated dialysate

Lanthanum

- Negligible biliary elimination
- Gastro-int. abs. of La not increased by citrate
- P binding not influenced by pH
- Faecal excretion of Al-contaminated dialysate

Behets GJ et al: Curr Opin Nephrol Hypertens 13, 403-409, 2004
Lanthanum Pharmacokinetics

Healthy subjects vs dialysis patients

Tissue deposition of lanthanum

Tissue lanthanum content
Median value after 12 weeks La carbonate loading, 2000 mg/kg/day

- NRF, Vehicle (n=9)
- CRF, Vehicle (n=9)
- NRF, La (n=4)
- CRF, La (n=5)

- Highest value: 8.5
- Highest value: 3.1

Serum content: 0.5-1.5 μg/L
Toxicity of aluminum is determined by its localization

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Level</th>
<th>Localization</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>high</td>
<td>Min. front*</td>
<td>established</td>
</tr>
<tr>
<td>Brain</td>
<td>low</td>
<td>?</td>
<td>established</td>
</tr>
<tr>
<td>Liver</td>
<td>high</td>
<td>lysosomes</td>
<td>absent</td>
</tr>
<tr>
<td>Parathyroid</td>
<td>relatively low</td>
<td>secretory granules lysosomes</td>
<td>interference with the PTH release</td>
</tr>
</tbody>
</table>


Where is lanthanum localized?
No evidence of toxicity

Bone lanthanum levels in treated ESRD patients

Damment SJ & Shen V: Clin Nephrol 67: 127-137, 2005

Lanthanum carbonate as a phosphate binder

Highest concentration tested in animals (90µg/g) No Toxicity

15 year projection
All absorbed drug into bone
No clearance (46µg/g)
Deposition of lanthanum in bone

Extremely low La levels require sensitive detection methods

Principle of X-ray fluorescence

Typical X-ray fluorescence spectrum of bone sample

ESRF - The European Synchrotron Radiation Facility, Grenoble

Lanthanum is located at the outer edge of calcified bone

Normal bone

Rats loaded with 2000 mg/kg/day lanthanum carbonate for 12 weeks

Deposition of lanthanum in bone

Different localisation of lanthanum in bone

Patient 03/2493:
Treatment: 4 years
Bulk Bone La: ± 8 µg/g
Fluorescence ratio
La/Ca: 0.01
La content:
0.099 mol%

Deposition of lanthanum in bone

Lanthanum is unlikely to interfere with Ca-apatite crystal, even when concentrated in 1% of bone volume.

La distributed throughout the bone

La concentrated in 1% of bone volume

Maximal bone La concentration after 4 y: 10 µg/g
Molecular weight 139 Da

Ca-apatite crystal

Aluminum
Mw: 27
Bone conc: 50-200 µg/g
= 1850-7400 nmol/g

1 La / 50 000 Ca
1 La / 500 Ca
1 La / 50 000 Ca
1 Al / 400 to 1600 Ca
1 Al / 4 to 16 Ca

No effect

Ca-apatite crystal
Open-label multicentre randomized prospective controlled study in dialysis patients

A total of 98 patients (age 55 ± 14.3 y; 59 males) recruited from various dialysis centres in 12 countries.

In 63 of them a histomorphometric analysis of baseline and follow-up bone biopsies was performed.

Patients discontinued:
- Transplantation (n=10)
- Death (n=11)

Maximal dose:
- Lanthanum carbonate: 3750 mg/day
- Calcium carbonate: 9000 mg/day

Bone Formation Rate
(µm²/mm²/day)

Osteoid Area (%)

Histologic classification of renal osteodystrophy

Normal

Adynamic

Mild lesion*

Osteitis fibrosa*

Mixed lesion

Osteomalacia

*: both classified as hyperparathyroidism

: with fibrosis

Normal bone

Adynamic bone

Osteomalacia

Mixed lesion

Osteitis fibrosa
Lanthanum carbonate as a phosphate binder

One year lanthanum treatment does not induce low bone turnover

**Calcium**

- Hyperparathyroidism
- Mixed
- Normal
- Adynamic bone
- Osteomalacia

Baseline: n=30

One year: n=30

**Lanthanum**

- Hyperparathyroidism
- Mixed
- Normal
- Adynamic bone
- Osteomalacia

Baseline: n=33

One year: n=33

---

Effects of sevelamer vs calcium carbonate on renal osteodystrophy

Adapted from Ferreira A et al., J Am Soc Nephrol 19: 405-412, 2008
Tissue deposition of lanthanum

Tissue lanthanum content
Median value after 12 weeks La carbonate loading, 2000 mg/kg/day

- NRF, Vehicle (n=9)
- CRF, Vehicle (n=9)
- NRF, La (n=4)
- CRF, La (n=5)

Serum content: 0.5-1.5 μg/L
Transcellular transport of lanthanum in liver

Transmission electron microscopy of liver tissue


F. Roels
Electron Energy Loss Spectroscopy (EELS) of liver tissue of lanthanum loaded rats (dose: 0.3 mg/kg/day IV, 4 weeks)

Example of a HRTEM image of a nanoparticle in a granular lysosome

HRTEM=high resolution transmission electron microscopy

Crystallographic nature
Interplanar spacing of 0.30 ± 0.02
Lanthanum phosphate structure (LaPO4)
Lattice resolution

Bervoets A. et al:
Kidney Int (in press 2008)
Transmission electron microscopy of liver tissue of **lanthanum loaded rats** (dose: 0.3 mg/kg/day IV, 4 weeks)


F. Roels
Transcellular transport of lanthanum in liver

Lanthanum uptake in hepatocyte

Transcellular transport of lanthanum in liver

No accumulation  Transcellular Transport

Liver handling of lanthanum

loading

Study LAN 05
Wistar rats
Males
Number/time point = 6
Dose = 1000mg/kg/day La₂(CO₃)₃
Route = oral gavage
Treatment period = 20 weeks
Samples = 1 day, 1, 3, 6, 12, 26 weeks loading
Values = mean ± SD; n=6

unloading

Study SPD0099
Sprague-Dawley rats
Pooled sexes (male + female)
Number/time point = 12
Dose = 1500mg/kg/day La₂(CO₃)₃
Route = oral gavage
Treatment period = 4 weeks
Samples = 4, 26 weeks after cessation of dosing
Values = mean ± SD; n=12

*: p<0.05 vs. NRF
#: p<0.05 vs. previous time point

Liver concentrations of some lysosomally-stored metals (nmol/g)

**La**
- **Rat**
  - 3% La diet 110d
  - 9-20 nmol/g
- **Human**
  - dialysis
  - 4-12 nmol/g

**Fe**
- **Rat**
  - background:
  - 2700 ± 200
    - (Park, 1987)
  - 280 ± 24*
    - (Haywood, 1985)
- **Human**
  - background:
  - 300 – 800*
    - (Brewer, 1988)
  - 300 – 800
    - (Nuttal, 2003)
- **Human**
  - alcohol liver dis.:
  - 1400 ± 700*
    - (Basset, 1996)
  - 32000
    - (Nuttal, 2003)

**Cu**
- **Rat**
  - background:
  - 279 ± 55*
    - (Haywood, 1980)
  - 280 ± 24*
    - (Haywood, 1985)
- **Human**
  - background:
  - 300 – 800*
    - (Brewer, 1988)
  - 860
    - (Nuttal, 2003)
- **Human**
  - dialysis
ecephalopathy:
  - 15
    - (Berlyne, 1972)
  - 150 ± 60
    - (Alfrey, 1980)

**Al**
- **Rat**
  - background:
  - 15
    - (Berlyne, 1972)
- **Human**
  - background:
  - 150 ± 60
    - (Alfrey, 1980)
- **Human**
  - dialysis
ecephalopathy:
  - 11000 ± 800
    - (Alfrey, 1980)

* Dry weight (otherwise all values are wet weight)
Lanthanum carbonate treatment, for up to 6 years, is not associated with adverse effects on the liver in patients with chronic kidney disease stage 5 receiving hemodialysis.
No Hep+ patients had elevated bilirubin levels and Hepatic enzymes were similar in both groups.
Absence of deposition of lanthanum in brain

Unquantifiable brain lanthanum levels in rats with normal renal function

Plasma lanthanum concentration 1560 ng/mL (>1500 times human Cmax)

Rat NRF
Oral gavage
Treatment period: 4 weeks
Dose: 1500 mg/kg/day
N=12, Median, 25th & 75th %

Rat NRF
Intravenous bolus
Treatment period: 4 weeks
Dose: 3, 30 or 300 μg/kg/day
N=12, Median, 25th & 75th %

Shire Studies: SPD0099, SPD0102

*JASN*; 14; 205A; ABSTRACT
Lanthanum concentrations
2499 ± 3754 ng/g
Genzyme-sponsored study

Lowest limit of quantification: 6 ng/g
Cognitive deterioration not accelerated

- Deterioration in cognitive function scores similar in patients treated with Fosrenol® or standard therapy

![Graph showing cognitive function scores over time](image)

<table>
<thead>
<tr>
<th>Month</th>
<th>Fosrenol® (n)</th>
<th>Standard therapy (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>174</td>
<td>178</td>
</tr>
<tr>
<td>3.5</td>
<td>153</td>
<td>153</td>
</tr>
<tr>
<td>6</td>
<td>121</td>
<td>143</td>
</tr>
<tr>
<td>12</td>
<td>89</td>
<td>121</td>
</tr>
<tr>
<td>18</td>
<td>63</td>
<td>93</td>
</tr>
<tr>
<td>24</td>
<td>47</td>
<td>77</td>
</tr>
</tbody>
</table>

Altmann P et al., Kidney International; in press
Kidney Bone Disease
What happens when the kidney fails?

- Progression of kidney damage >> mineral metabolism
- Bone histology in ESRF
- Concept of calcium loading in CKD
- Non-calcium containing phosphate binders
- Lanthanum: a safe phosphate binder?

- Lanthanum and the calcium loading concept
Non calcium containing phosphate binders

Renagel (n=172)

Lanthanum (n=682 La, n=677 controls)


Effect of phosphate binder

- Bone Demineralization
- Osteomalacia


Urinary P ↓↓
Urinary Ca ↑
Stool 490 mg/d

Absorption of Ca ↑↑
Excretion of P ↑↑

GI intake 1400 mg/d

Digestive juice phosphorus 210 mg/d

Serum Phosphorus (Pi) ↓
2.4-5 mg/dl
0.65-1.4 mmol/L

Formation 210 mg/d

Resorption of P and Ca

DIALYSIS PATIENT
Effect of manipulating serum phosphorus with phosphate binder on circulating PTH and FGF23 in renal failure rats


Effects of (a) continuous and (b) intermittent treatment with sevelamer on serum phosphorus (left) and calcium (right) levels
Mechanism of epithelial Ca\(^{2+}\) transport,

Calcium absorption across epithelia
Molecular identification of the apical $\text{Ca}^{2+}$ channel in 1,25-dihydroxyvitamin D3-responsive epithelia


La dose: 0.5 nM

Serum La = 3-15 nM

$La > 99\%$ bound to serum proteins

Free La < 0.03-0.15 nM

NO Calcium Channel Blocking Effect

Functional characterization of the epithelial $\text{Ca}^{2+}$ channel
Incidence of hypercalcaemia based on a recent literature survey

Hutchison A et al. Nephron Clin Pract 2005;100:8–19
Why do we need a choice for non-calcium phosphate binders?

- **Historical**
  - Al OH₃  ❌ Toxicity (Blood, Brain & Bone)
  - Ca CO₃  ❌ Toxicity (Cardiovascular Disease)

- **Current**
  - Ca CO₃  ❌ Toxicity (Cardiovascular Disease)

- **Newer**
  - Sevelamer
  - Lanthanum

Choice!
Why Non Calcium containing phosphate binders

Lack of toxicity  
the aluminum story  
Calcium overload calcifications

Efficacy of Lanthanum , Sevelamer, as phosphate binders

Calcium balance La versus Sevelamer

Pill burden
People Involved

**University of Antwerp, Belgium**
- BEHETS Geert
- BERVOETS An
- DAMS Geert
- DAUWE Simonne
- DE BEUF Annelies
- DE BROE Marc
- DE WEERDT Dirk
- D’HAESE Patrick
- GERYL Hilde
- HUFKENS Annemie
- LAMBERTS Ludwig
- MARIJNISSEN Rita
- NEVEN Ellen
- PERSY Veerle
- SPAEPEN Gie
- VERBERCKMOES Steven
- VERHULST Anja
- VERVAET Benjamin

**Shire Pharmaceuticals, UK**
- DAMMENT Stephen
- STOKES Diana
- PENNICK Michael
- ROELS Frank
  *Pathology, Univ. Ghent, Belgium*
- SCHRYVERS Nick, YANG Zhiqing
  *Physics, Univ. Antwerp, Belgium*
- SUSINI J., SALOMÉ M.,
  *European Synchrotron Radiation Facility, Grenoble, France*
- DENTON J.
  *Musculoskeletal Res., Univ. Manchester, UK*
- McLEOD C., COX A.
  *Analytical Sc., Univ. Sheffield, UK*
- BLUST R., SELENS M.
  *Biology, Univ. Antwerp, Belgium*
Vascular calcification
Experimental models of chronic renal failure

- Adenine-induced chronic renal failure
  - Not suitable to study renal histology
  - Reproducible, moderate CRF: serum creatinine $\approx 2.5 - 3$ mg/dl
  - Lipid metabolism disturbances

Adenine-rich diet

APRT Adenine Phosphoribosyltransferase

Adenine + PRPP $\rightarrow$ AMP
Phosphoribosylpyrophosphate

Xanthine dehydrogenase

2,8-dihydroxy adenine

Crystalluria
Nephron destruction
Interstitial fibrosis
Renal failure


Katsumata et al., Kidney Int 2003
Adenine-low protein CRF rat model

Time-dependent increase of osteochondrocyte bone markers in association with the calcification process

Effect of La on uremia-related vascular calcification

Renal function

- CTL
- La 1%
- La 2%

Creatinine clearance (ml/min/100 g)

Creatinine (mg/dl)

Urea (mg/dl)

Weeks: -2, 0, 2, 5, 8

*: p<0.05 vs. week 0
*:* p<0.05 vs CTL

Neven NDT 2009
Effect of lanthanum carbonate on adenine induced vascular calcification

Neven et al. 2009   NDT Jan

#: p<0.05 vs. La 1%
°: p<0.05 vs week 0; *: p<0.05 vs CTL
Intervention

Vascular calcification

Effect of La on uremia-related vascular calcification

HISTOMORPHOMETRY

Von Kossa positivity (area %)

<table>
<thead>
<tr>
<th></th>
<th>Aorta</th>
<th>A. Carotis</th>
<th>A. Femoralis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=19</td>
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<tr>
<td>CRF La 1%</td>
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</tr>
<tr>
<td>N=20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRF La 2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=19</td>
<td></td>
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</tbody>
</table>

CALCIUM CONTENT

mg/g wet tissue

<table>
<thead>
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<td>N=20</td>
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<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=19</td>
<td></td>
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</tr>
</tbody>
</table>

#: p<0.05 vs. La 1%

NDT 2009

Osterix

Sox9
p<0.05 versus week 0
p<0.05 versus untreated CRF group at the same time point
° p<0.05 versus week 0
* p<0.05 versus untreated CRF group at the same time point
° p<0.05 versus week 0
* p<0.05 versus untreated CRF group at the same time point
° p<0.05 versus week 0
* p<0.05 versus untreated CRF group at the same time point
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