CKD-MBD after renal transplantation

Pieter Evenepoel
University Hospitals Leuven
Leuven - Belgium

Madrid, 2013
Disclosure of Interests

• Amgen: consultancy, research grant, honoraria, sponsored education
• Shire: honoraria, sponsored education
• Sanofi-Genzyme: research grant
CKD-MBD

Renal Transplantation

CKD stage 1-5

CKD stage 5D
Posttransplant CKD-MBD

Serum Creatinine

MBD

Renal transplantation

Persistent

Time

1 yr

Evenepoel Sem Nephrol 2013
Pretransplant CKD-MBD

CAC: At time of Tx, Evenepoel, unpublished data

- Low turnover
- Normal turnover
- High turnover

Evenepoel, unpublished data
<table>
<thead>
<tr>
<th>Immunosuppressive Agent</th>
<th>Effect on Bone Mineral Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>Effect on osteoblasts: decreases bone formation by inducing apoptosis, inhibiting function, and decreasing collagen synthesis. Effect on osteoclasts: increases bone resorption through osteoclast activation by upregulation of RANKL/OPG; systemic effects include decreased gastrointestinal absorption of calcium, increased renal calcium wasting (hypogonadism, myopathy, avascular necrosis)</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>Controversial effect: in vitro appears to inhibit bone resorption; in vivo appears to increase bone resorption, leading to bone formation; promote renal Mg leak; promote calciuria</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>No effect</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>No effect</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Controversial effect; in vitro appears to inhibit osteoclast differentiation; promotes renal phosphate leak</td>
</tr>
<tr>
<td>Evirolimus</td>
<td>Controversial effect; in vitro appears to inhibit osteoclast formation, activity, and differentiation</td>
</tr>
</tbody>
</table>

Adapted from Alshayeb et al. AJKD 2013
Posttransplant CKD-MBD

Serum Creatinine

Rena transplantation

MBD

Persistent

De novo

immunosuppression

Time

1 yr

Evenepoel Sem Nephrol 2013
Posttransplant CKD-MBD

- Laboratory abnormalities
- Bone disease
- Vascular calcification
- Treatment
Lab abnormalities

- Fibroblast Growth Factor 23
- 1,25 Dihydroxyvitamin D
- Parathyroid Hormone
- Phosphate

Graph showing changes in analyte concentrations over time post-transplant.

- Time post-transplant:
  - 0 months to 3 months
  - 3 months to >12 months

- Glomerular filtration rate:
  - >90 ml/min/1.73m²
  - 75 to 60 ml/min/1.73m²
  - 45 to 30 ml/min/1.73m²
  - <30 ml/min/1.73m²

- Analyte concentrations:
  - >10,000
  - 1,000
  - 90
  - 60
  - 30
  - 4

- Dialysis highlighted on the graph.
Bonarek et al. KI 1999 (n=11)
Posttransplant HPT: prevalence

Optimal PTH in renal transplant recipients remains a black box.

Lack of uniform definition of HPT.

n=201; 2004-2006

Evenepoel et al. data on file
Pathophysiology of persistent/inappropriate HPT

- Regression of parathyroid hyperplasia is a time-consuming process (low cell turnover and long life span of parathyroid cells)
- Clonal (autonomous) growth: less sensitive to normal feedback mechanisms
- Low/inappropriate low level of 25(OH)VitD and 1,25(OH)_2VitD
Risk factors for persistent/inappropriate HPT

- At time of transplantation:
  - Severe HPT as evidenced by high pre-transplant serum level of iPTH, calcium, phosphorus and alkaline phosphatases or therapy with cinacalcet
  - Long dialysis vintage
  - Vit D receptor polymorphisms (bb>BB)?

Torres et al. NDT 1998;suppl3:94-97
Evenepoel et al. NDT 2004;19:1281-7
Reinhardt et al. NDT 1998;13:436-442
Evenepoel et al Clin Transplant 2012
Torregrossa et al Transplant Proc 2009
Risk factors for persistent/inappropriate HPT

Mineral metabolism in renal transplant recipients discontinuing cinacalcet at the time of transplantation: a prospective observational study

Posttransplant HPT

- Persistent HPT
- De Novo secondary HPT

Serum Creatinine

MBD

Rena transplantation

immunosuppression

De novo
Posttransplant de novo sHPT

Persistent HPT

De Novo secondary HPT

Appropriate
- To overcome endorgan resistance
- To maintain normophosphatemia
- To maintain normocalcemia

Inappropriate

Disease

- Question mark

CKD-MBD Controversies Conference  |  October 25-27, 2013  |  Madrid, Spain
Posttransplant persistent HPT

Persistent HPT

Appropriate
- To overcome endorgan resistance
- To maintain normophosphatemia
- To maintain normocalcemia

Inappropriate

Manifested by:
- Hypophosphatemia
- Hypercalcemia

Disease
Posttransplant HPT & hypophosphatemia

Persistent HPT

Appropriate
- To overcome endorgan resistance
- To maintain normophosphatemia
- To maintain normocalcemia

Inappropriate

Manifested by:
- Hypophosphatemia
- Hypercalcemia

Disease
PO$_4$ nadir: 1.5 ± 0.5 mg/dL; at day 27±19

Evenepoel et al. CJASN 2009
Hypophosphatemia, defined as $\text{PO}_4 < 2.3 \text{ mg/dL} (0.74 \text{ mmol/L})$

Period

- M3: 26.8%
- M12: 8.8%

Evenepoel et al. CJASN 2008; Evenepoel data on file
Renal Phosphorus leak

Fractional excretion of phosphate: 70%

Renal Phosphorus leak

PTH

FGF23

Synergism

Bhan et al. Kidney Int 2006

Evenepoel et al. AJT 2007
Posttransplant HPT & hypercalcemia

Persistent HPT

Appropriate
- To overcome endorgan resistance
- To maintain normophosphatemia
- To maintain normocalcemia

Inappropriate
- Manifested by: Hypophosphatemia
- Hypercalcemia

Disease
Calcium

Evenepoel et al. CJASN 2009; Evenepoel, data on file

N=201
Hypercalcemia: prevalence

Hypercalcemia, defined as Albumin corrected tCa >10.3 mg/dL; n=201
Wide variation:

- Differences in diagnostic criteria
- Differences in interval since transplantation
- Differences in study era (e.g. before and after K/DOQI guidelines on mineral metabolism)
Hypercalcemia: diagnostic criteria

Evenepoel et al CJASN 2010

Hypercalcemia:
- tCa > 10.3 mg/dL (UNL) with iCa > 1.32 mmol/L at month 3 (13.1%), month 12 (13.1%)
- tCa > 10.3 mg/dL (UNL) with iCa > 1.29 mmol/L (UNL) at month 3 (40.7%), month 12 (28.5%)
- tCa > 10.3 mg/dL (UNL) with iCa > 1.29 mmol/L (UNL) at month 3 (58.6%), month 12 (44.8%)

Prevalence (%)
Posttransplant calcium metabolism/balance

Inappropriately high PTH levels

- GI calcium absorption?
- Calcitriol
- FGF23
- 1-α-hydroxylase
- Calcitriol
- GC, CNI
- Tubular Ca reabsorption
- Bone release↑↑
- Calcium balance?

Evenepoel et al. CJASN 2009
Lee et al AJN 2011
Lab abnormalities

- Fibroblast Growth Factor 23
- 1,25 Dihydroxyvitamin D
- Parathyroid Hormone
- Phosphate
FGF-23

-94.7% 

Evenepoel et al. CJASN 2008
Evenepoel et al. AJT 2007

Bhan et al. Kidney Int 2006
Vitamin D

**Calcidiol**

1,25 (OH)\(_2\)D\(_3\)

- **PTH**
- **FGF-23**

- **1-α-hydroxylase**
- **24-hydroxylase**

- **24,25 (OH)\(_2\)D\(_3\)**
- **1,24,25 (OH)\(_3\)D\(_3\)**

*Wesseling-Perry Pedr Nephrol 2013*
*Evenepoel CJASN 2008 2007*
Alkaline Phosphatases

n = 129, mean ± SEM, screat < 2 mg/dL, iPTH 150 pg/ml

Reinhardt et al. NDT 1998
Lab abnormalities and patient-level outcomes

Observational data, associations:

<table>
<thead>
<tr>
<th></th>
<th>Fractures</th>
<th>Graft survival</th>
<th>CVD</th>
<th>Patient survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH</td>
<td>pos 1, 2, 6</td>
<td>0&lt;sup&gt;3,7&lt;/sup&gt;</td>
<td>Pos: IMT&lt;sup&gt;4&lt;/sup&gt;, arterial stiffness&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0&lt;sup&gt;3,7&lt;/sup&gt;</td>
</tr>
<tr>
<td>FGF23</td>
<td>?</td>
<td>neg&lt;sup&gt;3&lt;/sup&gt;</td>
<td>?</td>
<td>neg&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

1. Perrin et al. AJT 2013
2. Perrin et al. AJT 2013
3. Wolf et al. JASN 2011
4. Suwelack AJH 2001
6. Yamamoto et al. JBMR 2013
7. Molnar CJASN 2012
Posttransplant CKD-MBD

- Laboratory abnormalities
- Bone disease
- Vascular calcification
- Treatment
# Bone histomorphometry

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>interval</th>
<th>T (H/N/L, %)</th>
<th>M (L, %)</th>
<th>V (L, %)</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rojas</td>
<td>20</td>
<td>1-6 m</td>
<td>↓</td>
<td></td>
<td></td>
<td>impaired osteoblastogenesis and early osteoblast apoptosis</td>
</tr>
<tr>
<td>Julian</td>
<td>20</td>
<td>6 m</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rolla</td>
<td>20</td>
<td>8.3 yr</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>GC dose correlates inversely with V and T</td>
</tr>
<tr>
<td>Monier-Faugere</td>
<td>57</td>
<td>5,6 yr</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Carlini</td>
<td>25</td>
<td>7,5yr</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>High bone resorption, coexisting with a low bone formation rate and delayed mineralisation time (uncoupling of bone resorption and formation)</td>
</tr>
<tr>
<td>Lehmann</td>
<td>57</td>
<td>4 yr</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Neves</td>
<td>27</td>
<td>2 yr</td>
<td>26/48/26</td>
<td>48</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

Posttransplant bone metabolism

Osteocyte

Sclerostin

PTH

\[ \text{NaPiIIa/c} \downarrow \]

Hypophosphatea

FGF23\[ \uparrow \]

Osteoblast

Osteoclast

RANKL\[ \uparrow \]

BONE FORMATION\[ \uparrow \]

BONE RESORPTION\[ \uparrow \]

Hypercalcemia

Rojas et al., Kidney Int 2003; Evenepoel Sem Nephrol 2013
(a) BMD

- wide variation
- pronounced loss during the first year, most probably related to high steroid exposure in this period
- Less pronounced loss in recent cohorts (0.1-5.7%, LS), most probably reflecting less corticosteroid exposure
- Varies across skeletal sites
### Bone abnormalities and patient-level outcomes

<table>
<thead>
<tr>
<th></th>
<th>Fractures</th>
<th>Graft survival</th>
<th>Patient survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone histomorphometry</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>(a)BMD</td>
<td>neg&lt;sup&gt;1&lt;/sup&gt;</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Bone biomarker</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

1. Akaberi et al. AJT 2008
Posttransplant CKD-MBD

- Laboratory abnormalities
- Bone disease
- Vascular calcification
- Treatment
## Vascular calcification

<table>
<thead>
<tr>
<th>Author/group</th>
<th>Schankel</th>
<th>Mazzoferro</th>
<th>Moe</th>
<th>Oschatz</th>
<th>Seyahi</th>
<th>Bargnoux</th>
<th>Maréchal</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>82</td>
<td>41</td>
<td>23</td>
<td>31</td>
<td>150</td>
<td>83</td>
<td>189</td>
</tr>
<tr>
<td>population</td>
<td>incident</td>
<td>prevalent</td>
<td>incident</td>
<td>incident</td>
<td>prevalent</td>
<td>Incident</td>
<td>prevalent</td>
</tr>
<tr>
<td>Age, male (%)</td>
<td>50, 62%</td>
<td>48, 61%</td>
<td>NA</td>
<td>53, 73%</td>
<td>39, 67%</td>
<td>51, 62%</td>
<td>53, 61%</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Ischemic cardiac disease</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Ischemic cardiac disease</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Baseline CAC %</td>
<td>67%</td>
<td>35%</td>
<td>69%</td>
<td>81%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline CAC score (mean/ median)</td>
<td>392/76</td>
<td>660/5</td>
<td>269/19</td>
<td>716/215</td>
<td>60/0</td>
<td>388/54</td>
<td>1617/195</td>
</tr>
<tr>
<td>Follow-up (yrs)</td>
<td>1.8</td>
<td>2.0</td>
<td>1.0</td>
<td>1.0</td>
<td>2.8</td>
<td>1.1</td>
<td>4.4</td>
</tr>
<tr>
<td>ΔCACpy (units)</td>
<td>+ 0.5 (median)</td>
<td>NA</td>
<td>0 (median)</td>
<td>+</td>
<td>+ 0.5 (median)</td>
<td>0 (median)</td>
<td>+11 (median)</td>
</tr>
<tr>
<td>ΔCACpy (%)</td>
<td>1.4 (median)</td>
<td>67.3 (mean)</td>
<td>NA</td>
<td>25 (mean)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progr Schankel</td>
<td>23%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>38%</td>
<td>NA</td>
<td>38%</td>
</tr>
<tr>
<td>Progr Hokanson</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>29%</td>
<td>26%</td>
<td>47%</td>
</tr>
<tr>
<td>Progr Sevrukov</td>
<td>NA</td>
<td>12%</td>
<td>NA</td>
<td>NA</td>
<td>28%</td>
<td>NA</td>
<td>49%</td>
</tr>
<tr>
<td>Determinants baseline</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Age, gender, PTH, dialysis vintage</td>
</tr>
</tbody>
</table>

### Determinants progression
- Baseline CAC, race, BMI, BP
- PTH, erythrocyte sedimentation rate
- NA
- Baseline CAC, smoking, dialysis vintage
- Baseline CAC, triglyceride level, Bisphosphonate use
- Baseline CAC
- Baseline CAC, phosphate, calcidiol

### Other relevant findings
- TX favorable affects but does not halt CAC progression
- Slower progression in TX as compared to HD patients
- Early increase, followed by stabilisation
- Progression similar to general population, slower than in HD

- Slower progression in TX as compared to HD patients
- Early increase, followed by stabilisation
- Progression similar to general population, slower than in HD
Vascular calcification

Brussels Renal Transplant Cohort (BRTC) study, n=189, FU 4.4 yrs

Independent determinants of progression: high age, high serum phosphate, low calcidiol, high baseline score

Hokanson:
- progression
- regression
- stabilization

Evenepoel, Jadoul (in preparation)
Vascular calcification and patient level outcomes

Observational data, associations:

<table>
<thead>
<tr>
<th>Vascular calcification</th>
<th>Fractures</th>
<th>CVE</th>
<th>Patient survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>( ? )</td>
<td>pos (^1,2)</td>
<td>( ? )</td>
<td>( ? )</td>
</tr>
</tbody>
</table>

Independent of age, gender, and CV history

1. Nguyen et al. NDT 2010
2. Claes et al. Transplant Int 2013
Posttransplant CKD-MBD

- Laboratory abnormalities
- Bone disease
- Vascular calcification
- Treatment
Treatment options

- Supplements: calcium, phosphorus, Vitamin D
- Parathyroid hormone suppression
  - Parathyroidectomy
  - Calcimimetics
- Antiresorptive agents
- Bone anabolics
- Steroid sparing/withdrawal
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Treatment effect</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>Replenish calcium PTH suppression</td>
<td>hypercalcemia?</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Replenish $\text{PO}_4$</td>
<td>Large doses required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limited efficacy ($\uparrow$FGF-23 and/or PTH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\bullet$ May promote nephrocalcinosis</td>
</tr>
<tr>
<td>Native Vit D</td>
<td>$\uparrow$GI Ca absorption $\downarrow$PTH (pleiotropic effects)</td>
<td>$\bullet$ hypercalcemia (origin?)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\bullet$ fracture risk ?: RCTs neg</td>
</tr>
<tr>
<td>Active Vit D</td>
<td>$\uparrow$GI Ca absorption $\downarrow$PTH $\uparrow$ BMD FN and LS (pleiotropic effects)</td>
<td>$\bullet$ hypercalcemia (origin?)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\bullet$ fracture risk:?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\bullet$ RCTs neg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\bullet$ meta-analysis (pos)</td>
</tr>
</tbody>
</table>

References:
Evenepoel Sem Nephrol 2013; Alshayeb, Josephson, Sprague AJKD 2013; Palmer Cochrane 2007; Stein et al. JCEM 2012 (solid organTx); Yu et al. Clin Tranplant 2012; Lieben et al. JCI 2012
Phosphate supplements

Prospective interventional study, n=32; initiation at month 41
Single arm: Na$_2$HPO$_4$: 1500 mg/d for 2 weeks Caravaca et al. NDT 1998

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCreat</td>
<td>1.23</td>
<td>1.23</td>
<td>NS</td>
</tr>
<tr>
<td>sPhos (mg/dL)</td>
<td>2.62</td>
<td>3.37</td>
<td>0.0001</td>
</tr>
<tr>
<td>sCa (mg/dL)</td>
<td>10.53</td>
<td>10.23</td>
<td>0.003</td>
</tr>
<tr>
<td>sBic (mEq/L)</td>
<td>24.6</td>
<td>23.8</td>
<td>0.003</td>
</tr>
<tr>
<td>sPTH (ng/L)</td>
<td>132</td>
<td>172</td>
<td>0.0001</td>
</tr>
<tr>
<td>uPhos (mg/d)</td>
<td>824</td>
<td>1668</td>
<td>0.0001</td>
</tr>
<tr>
<td>uCa (mg/d)</td>
<td>189</td>
<td>122</td>
<td>0.0001</td>
</tr>
<tr>
<td>FE phos (%)</td>
<td>29.5</td>
<td>48.0</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
Prospective randomized controlled interventional study
n=28 (1:1); initiation at month 1;
Arm A: NaCl, 12 weeks
Arm B: Na$_2$HPO$_4$: 300-900 mg/d, 12 weeks
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Treatment effect</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroidectomy</td>
<td>↑Po₄, ↓Ca, ↓PTH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(↑ BMD)</td>
<td>4-gland hyperplasia requires general anesthesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Transient hypocalcaemia due to “hungry-bone” syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Persistent hypoparathyroidism with sustained hypocalcaemia / low bone turnover</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Parathyromatosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No RCTs with hard endpoints</td>
</tr>
<tr>
<td>Calcimimetics</td>
<td>↑PO₄↓Ca, ↓PTH</td>
<td>• Risk of low bone turnover</td>
</tr>
<tr>
<td></td>
<td>(↑ BMD)</td>
<td>• No registration post-transplant/off-label</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No RCTs with hard endpoints</td>
</tr>
</tbody>
</table>

Evenepoel  Sem Nephrol 2013
Alshayeb, Josephson, Sprague AJKD 2013
Cinacalcet

**A**

Total calcium (mmol/l)

-52  -24  -12  -4  0  2  4  6  8  10  14  18  22  26  30

Cinacalcet treatment

**B**

Phosphate (mmol/l)

-52  -24  -12  -4  0  2  4  6  8  10  14  18  22  26  30

Cinacalcet treatment

Serra et al. NDT 2007

Serra et al. AJK 2008

Serra et al. AJT 2008
Cinacalcet

Serum calcium mg/dL

Pre-therapy values
Post-therapy values

Pre-therapy calcium
Post-therapy calcium

Plasma PTH pg/mL

Pre-therapy values
Post-therapy values

Cinacalcet
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Treatment effect</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>↓Ca, (↑PTH, ↓Po4), ↑ BMD</td>
<td>• risk of low bone turnover&lt;br&gt;• fracture risk:?&lt;br&gt;• RCTs neg;&lt;br&gt;• meta-analysis pos</td>
</tr>
<tr>
<td>Denosumab</td>
<td>↓Ca, (↑PTH, ↓Po4), ↑ BMD</td>
<td>• Risk of low bone turnover&lt;br&gt;Unknown immunological effects&lt;br&gt;No registration post-Tx</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>↑ coritcal bone ?</td>
<td>• Questionable efficacy</td>
</tr>
<tr>
<td>Steroid sparing</td>
<td>↑GI Ca absorption ↑BMD</td>
<td>• No RCTs</td>
</tr>
<tr>
<td>Correct metabolic acidosis/Mg depletion</td>
<td>↑HCO3, ↑Mg</td>
<td></td>
</tr>
</tbody>
</table>

Evenepoel  Sem Nephrol 2013; Alshayeb, Josephson, Sprague AJKD 2013; Stein et al. JCEM 2011
### Bisphosphonates

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grotz et al</td>
<td>80</td>
<td>Prospective placebo controlled; kidney recipients received either ibandronate or placebo at 3, 6, and 9 mo posttransplantation vs control group</td>
<td>Less bone loss, spinal deformation, and loss of body height in the ibandronate group during first y posttransplantation</td>
</tr>
<tr>
<td>Fan et al</td>
<td>26</td>
<td>Prospective placebo controlled; kidney recipients received either IV pamidronate or placebo at time of transplantation and 1 mo later; 17 patients had second DEXA at 4 y</td>
<td>Preserved BMD at lumbar spine and femoral neck in pamidronate group vs increased loss of BMD in placebo group during first y posttransplantation; preserved BMD at femoral neck in 4 y in pamidronate-treated group</td>
</tr>
<tr>
<td>Haas et al</td>
<td>20 (incident)</td>
<td>Prospective placebo controlled; kidney recipients received either zoledronic acid or placebo at baseline and 3 mo after transplantation, calcium citrate 1 g/d; creat &lt; 2 mg/dL.</td>
<td>Improved BMD in lumbar spine, stable BMD in femoral neck at 6 mo, T ↓ in both groups without increased risk of adynamic bone disease in the zoledronic acid–treated group</td>
</tr>
<tr>
<td>Coco et al</td>
<td>20 (incident)</td>
<td>Prospective, controlled; kidney recipients received either pamidronate at baseline, 1, 2, 3, 6 mo plus daily vitamin D (400 IU) /Ca^{2+} (500mg) vs vitamin D/Ca^{2+}, no GFR limitation</td>
<td>Preserved BMD in vertebral spine at 6 and 12 mo with increased risk of adynamic bone disease in pamidronate-treated group (all patients in pamidronate group vs 50% in control group)</td>
</tr>
<tr>
<td>Walsh et al</td>
<td>93 (incident)</td>
<td>Prospective, controlled; kidney recipients received either pamidronate at baseline, 1, 2, 3, 6 mo plus daily vitamin D (400IU)/Ca^{2+} (500 mg) vs vitamin D/Ca^{2+}, no GFR limitation</td>
<td>Preserved BMD in lumbar spine, total hip at 12 mo. Lower (NS) fracture rate in pamidronate group (6.4% vs 3.3 % per year)</td>
</tr>
<tr>
<td>Jeffery et al</td>
<td>117</td>
<td>Prospective, controlled; kidney recipients with osteopenia at baseline received either daily alendronate and Ca^{2+} vs calcitriol and Ca^{2+}</td>
<td>Improved BMD in lumbar spine and femoral neck in both groups, superior effect of alendronate on spine BMD</td>
</tr>
</tbody>
</table>
## Bisphosphonates

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Population</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>El-Agroudy et al (2005)</td>
<td>60</td>
<td>Prospective, controlled; kidney recipients with osteopenia or osteoporosis at baseline received either alendronate (5 mg/d) or alfacalcidol (0.5 µg/d) or calcitonin (100µL intranasally) vs control; calcium carbonate 0.5 g/d; creat &lt; 2mg/dL.</td>
<td>Alfacalcidol and alendronate improved BMD at both lumbar spine and femoral neck, while calcitonin improved BMD in lumbar spine only (at 1 year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nowacka-Cieciura et al (2006)</td>
<td>66</td>
<td>Prospective, controlled; kidney recipients with osteopenia or osteoporosis at baseline received either alendronate or risendronate or were drug free</td>
<td>Improved BMD in femoral neck in bisphosphonate-treated group at 12 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torregrosa et al (2007)</td>
<td>84</td>
<td>Prospective, controlled; kidney recipients with osteopenia at baseline received either weekly risendronate + daily vitamin D/Ca²⁺ or vitamin D/Ca²⁺ only</td>
<td>Increased BMD in lumbar spine at 1 y in risendronate-treated group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abediazar &amp; Nakhjavani (2011)</td>
<td>43</td>
<td>Prospective, controlled; kidney recipients with osteopenia at baseline were randomly assigned to either weekly alendronate (30 mg) + daily vitamin D (not specified) or daily vitamin D only</td>
<td>Alendronate increased BMD in distal radius and lumbar spine at 1 y (poor quality study)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamamoto (2013)</td>
<td>24</td>
<td>Prospective, controlled; kidney recipients with low BMD were prescribed weekly oral alendronate (35 mg); mean GFR 49 ml/min, 1.73m², no Vit D</td>
<td>Oral alendronate did not affect BMD in lumbar spine (after 2 yr) but suppressed bone turnover biomarkers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smerud (2012)</td>
<td>129</td>
<td>Randomized, double-blind, placebo-controlled study; kidney recipients (&lt;4 wk) received either ibendronate iv (3 mg, every 3 mo for 12 mo) or placebo; eGFR &gt; 30 ml/min, calcitriol (0.25 µg/d) + calcium carbonate (2.5 g)</td>
<td>Improved BMD in total femur and ultradistal radius but not in lumbar spine in ibendronate-treated patients at 12 mo. Suppression of bone formation markers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMD, bone mineral density; Ca²⁺, calcium; DEXA, dual-energy x-ray absorptiometry; IV, intravenous

Adapted from Alshayeb et al. AJKD 2013
Individualized therapy

Algorithm for treatment allocation after transplantation.

Mainra R, and Elder G J CJASN 2010;5:117-124
Kidney transplantation does not solve the problem of CKD-MBD

Posttransplant CKD-MBD is very heterogeneous and reflect prior MBD, de novo MBD, and the effects of immunosuppressive drugs

The pathophysiology of posttransplant CKD-MBD is ill-defined

Adequately designed and powered RCT addressing posttransplant CKD-MBD are scarce

Therapy should be focussed on controlling inappropriate persistent hyperparathyroidism, as reflected by simultaneous hypercalcemia and/or hypophosphatemia, and should be causal whenever possible

Therapy should be individualized
Research recommendations

• In depth experimental and clinical research to elucidate the pathophysiology of posttransplant CKD-MBD

• Balance studies to determine calcium, phosphorus and magnesium balance in (incident) renal transplant patients

• Adequately designed RCT to evaluate the efficacy of various established treatment strategies (and especially PTH suppression therapy) on surrogate and hard patient-level outcomes

• Define the value of laboratory abnormalities, bone imaging techniques and bone histomorphometry in predicting fractures