Posttransplant Bone Disease

Budapest
2007
Post-transplant bone disease

- 7 –10 % of kidney transplanted patients develop a fracture.

- The risk is higher in postmenopausal female transplanted patients.

- Diabetic, kidney and pancreas transplanted patients have a fracture risk of up to 45 %.

- Femoral head necrosis is seen in 3 %.

- Approx. 60% of the kidney transplanted patients have a significant reduction of BMD after transplantation.
Post-transplant bone disease

Disturbances in mineral metabolism:

- Persistent sec. HPT: >50%
- Hypercalcemia: ~50% <3 Mo, ~15% <2 years
- Hypophosphatemia: ~80% <4 Mo, ~40% <1 year
- Hypomagnesemia: ~40%
- Low vit. D: ~25%
Post-transplant hypercalcemia

- Incidence: 8.5 – 65 %

- Course: Spontaneous resolution, as only between 1.3 and 20 % later will need PTX.

- Pathogenesis:
  - persistent HPT
  - resolution of soft tissue calcifications
  - immobilization
  - high doses of glucocorticoids
  - hypophosphatemia
Tertiary HPT after renal transplantation

D’Alessandro AM et al, Surgery, 1989

773 patients

227 (29%) serum Ca\(^{++}\) > 10.5 mg/dl

156 (69%) resolution of hypercalcemia

56 (25%) persistent hypercalcemia

15 (7%) inadequate follow-up

14 (6%) PTX

42 (19%) further observation

All patients > 1 year post transplant
Post-transplant hypophosphatemia

Incidence: ~ 80 - 40 %

Causes:

- increased levels of PTH
- increased levels of phosphatonin?
- relative deficiency of 1,25(OH)₂D₃
- glucocorticoids
- cyclosporine/tacrolimus
Mazzola BL et al, Transpl. Int. 2003

Hypomagnesemia post-transplantation

Plasma ionized magnesium and its urinary excretion in transplant recipients (> 12 mo.) treated with (circle) (n=46) or without (square) (n=9) cyclosporine and in healthy subjects (diamond) (n=31).
# Post transplant PTH and calcitriol levels in 61 patients

*de Sevaux RGL et al, Nephron 2003*

<table>
<thead>
<tr>
<th>Time after transplantation, months</th>
<th>Baseline</th>
<th>1</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>24</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR ml/min.</td>
<td></td>
<td>55±17</td>
<td>60±18</td>
<td>67±20</td>
<td>65±20</td>
<td>66±22</td>
<td></td>
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<tr>
<td>PTH pmol/l</td>
<td>33±35</td>
<td>14±9</td>
<td>11±6</td>
<td>10±6</td>
<td>11±9</td>
<td>11±9</td>
<td>1.0-6.5</td>
</tr>
<tr>
<td>25(OH)D ng/ml</td>
<td>32±19</td>
<td>23±12</td>
<td>23±8</td>
<td>26±11</td>
<td>26±10</td>
<td>23±9</td>
<td>10-34</td>
</tr>
<tr>
<td>1,25(OH)$_2$D pmol/l</td>
<td>44±25</td>
<td>51±27</td>
<td>72±34</td>
<td>95±50</td>
<td>102±43</td>
<td>85±35</td>
<td>80-200</td>
</tr>
</tbody>
</table>
Rapid decline in PTH after kidney transplantation
# PTX after a successful renal transplantation

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No of patients</th>
<th>PTX %</th>
<th>Follow-up, Mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geis</td>
<td>1973</td>
<td>18</td>
<td>20.0</td>
<td>12</td>
</tr>
<tr>
<td>David</td>
<td>1982</td>
<td>4</td>
<td>6.3</td>
<td>-</td>
</tr>
<tr>
<td>Diethelm</td>
<td>1985</td>
<td>5</td>
<td>1.3</td>
<td>72</td>
</tr>
<tr>
<td>Garvin</td>
<td>1989</td>
<td>7</td>
<td>7.0</td>
<td>2-44</td>
</tr>
<tr>
<td>D’Alessandro</td>
<td>1991</td>
<td>15</td>
<td>1.8</td>
<td>48</td>
</tr>
<tr>
<td>Vlcek</td>
<td>1992</td>
<td>32</td>
<td>5.9</td>
<td>228</td>
</tr>
<tr>
<td>Botha</td>
<td>1993</td>
<td>37</td>
<td>3.3</td>
<td>120</td>
</tr>
<tr>
<td>Dotzenrath</td>
<td>1995</td>
<td>22</td>
<td>5.1</td>
<td>69</td>
</tr>
<tr>
<td>Neonakis</td>
<td>1995</td>
<td>21</td>
<td>4.5</td>
<td>120</td>
</tr>
<tr>
<td>Schmid</td>
<td>1997</td>
<td>37</td>
<td>1.4</td>
<td>156</td>
</tr>
<tr>
<td>Gwinner</td>
<td>2005</td>
<td>12</td>
<td>5.6</td>
<td>36</td>
</tr>
<tr>
<td>Evenepoel</td>
<td>2007</td>
<td>90</td>
<td>8.7</td>
<td>63</td>
</tr>
</tbody>
</table>
Ninety subjects required a PTX in the post-transplant period. This corresponds to an overall PTX rate of 8.89 per 1000 person-years at risk.

Kaplan–Meier survival curve of renal recipients (1989–2004) using parathyroidectomy as the end point. The patients were censored at the time of death, graft failure, loss of follow-up or end of follow-up (1 January 2004).
Impact of PTX on renal graft function after a successful kidney transplantation:

- 1 mo after PTX a significant increase of serum creatinine was observed from 1.76 ± 0.63 to 1.91 ± 0.72 mg/dl (N=90).
- 6 mo after PTX serum creatinine increased significantly from 1.75 to 2.13 mg/dl (N=32)
- GFR was however stable after > 4 yr and graft survival similar in PTX patients and controls (N=90).
Comparison of graft survival between patients requiring parathyroidectomy ($n = 90$) and a matched cohort of renal allograft recipients ($n = 180$).
Graft survival with and without PTX

Post-transplant bone disease
Free of fracture Kaplan-Meier survival curves for all patients (n=193).
Free of fracture Kaplan-Meier survival curves for IDDM (n=35) and non-DM patients (n=158), in relation to number of years after transplantation (dated from the first transplantation, when retransplanted).
Time to hospitalization for avascular necrosis in U.S. renal transplant recipients from July 1, 1994 to 1998. $N = 42,096$ patients,
Changes in BMD of the lumbar spine in 20 renal transplanted patients
Bone mineral density at 12 months post-transplantation (n=44).
Smets YFC et al, KI 2004

Long-term follow-up study on bone mineral density and fractures after simultaneous pancreas-kidney transplantation.
Comparison of static histomorphometric parameters of 11 paired bone biopsies performed at the times of transplantation (pre-Tx) and 38 ± 17 days after transplantation (post-Tx).
Representative microphotograph of bone biopsies showing cell apoptosis by the TUNEL method.

(A) TUNEL-positive osteoblasts by direct immunofluorescence staining in mixed bone disease. (B) Apoptotic bodies in the proximity of osteoid seams in osteomalacia. (C) Apoptotic osteocytes. (D) TUNEL-positive cells in the proximity of osteoid seams by immunoperoxidase staining in osteitis fibrosa showing. BT is bone trabeculae.

Osteoblast number per tissue surface in bone biopsies of patients showing osteoblast apoptosis (Apoptosis, $N = 9$) compared with those without evident apoptosis (No apoptosis, $N = 11$).
(A) Posttransplant serum phosphorus levels in patients showing apoptosis compared with patients without osteoblast apoptosis in posttransplant bone biopsies. (B) Relationship between serum phosphorus and apoptosis of osteoblasts.
Correlation between serum PTH levels and osteoblast surface.

(A) between pretransplant serum PTH and posttransplant osteoblast surface.
(B) between posttransplant serum PTH and posttransplant osteoblast surface.
Correlation between the posttransplant cumulative dose of glucocorticoids and osteoblast surface.
**Effect of steroid withdrawal 3 mo. post-transplant.**

<table>
<thead>
<tr>
<th>Lumbar spine</th>
<th>-Steroid n=10</th>
<th>+Steroid n=17</th>
<th>+Steroid/+MMF n=9</th>
<th>+Steroid/-MMF n=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD %</td>
<td>1.9±4.2*</td>
<td>-1.4±3.2</td>
<td>-1.6±4.0</td>
<td>-1.1±1.9</td>
</tr>
</tbody>
</table>

Evaluated 6 mo. post-transplant.

van den Ham EC et al, Transpl Int 2003
X-ray absorptiometry 12 months post-renal transplantation, expressed as the change of the initial values. tacrolimus (n=7), cyclosporin (n=19).
Immunosuppressiva with no effect on bone

• **Azathioprine**  
  Bryer HP et al. JBMR 10, 1995

• **Mycophenolate mofetil**  
  Dissanayake, IR et al, Transplantation 65, 1998

• **Rapamycin**  
  Goodman GR et al, JBMR 16, 2001
Post-transplant bone disease
pre-transplant risk factors 1:

1. Previous history of renal osteodystrophy:
   a. sec. HPT
   b. osteomalacia – hypovitamin D
   c. mixed bone disease
   d. adynamic bone disease
   e. aluminum intoxication

2. Drug treatment with:
   a. active vitamin D analogs and calcium
   b. previous steroid treatment or
   c. immunosuppressive drugs
   d. anticonvulsant therapy
Post-transplant bone disease
pre-transplant risk factors 2:

3. Other factors:
   - immobilisation
   - malnutrition
   - Impaired gonadal status
   - history of fractures
   - history of musculoskeletal symptoms

4. Low BMD

5. Renal diagnosis - DM? etc

6. Type and duration of dialysis
Post-transplant bone disease

post-transplant risk factors

- Low GFR post-transplant
- Immunosuppressive therapy:
  - Glucocorticoids
  - Cyclosporin A / Tacrolimus
- Persistent 2. HPT/ 3. HPT
- Hypercalcemia
- Hypophosphatemia/ hypomagnesemia
- Loop diuretics
- Persistent hypogonadism
Treatment with $1\alpha$-hydroxy vitamin D (0.25 µg/day) and calcium (1000 mg/day) reduces bone loss after renal transplantation (n=111).
Effect of renal transplantation on BMD at the lumbar spine. Changes in BMD in (A) control patients and (B) pamidronate treated patients. (n=26)
Long-term effects (>24 months) on BMD at the femoral neck of pamidronate given at the time of renal transplantation

n=17

Fan SL et al
KI 63:2275, 2003
Bone loss at femoral neck in patients with (n=33) and without rejection (n=47), treated with • (n=11) or without ibandronate iv. □ (n=22)
Cohen A et al, JBMR 2004
Management of bone loss after organ transplantation
Treatment of decreased BMD in long-term (~9 years) renal transplant recipients: a randomized prospective one year trial of calcitriol (n=51) versus alendronate (n=46)

Jeffery JR et al, Transplantation 76, 2003
Coco M et al, JASN 2003

n=31
n=28

Vertebral BMD

Bone histomorphometry (n=14)

pamidronate ----- control ______
Nephrotic syndrome after treatment with pamidronate.

Markowitz GS et al
AJKD 2002

(A) Glomerulus displaying **global collapse** of the glomerular tuft with marked podocyte swelling and proliferation, forming a pseudocrescent.

(B) Glomerulus with **obliteration of capillary lumina** caused by global glomerular basement membrane collapse.

(C) Widespread **tubular abnormalities**, including microcyst formation, luminal ectasia, and epithelial simplification.
Treatment of hypercalcemia with cinacalcet in renal transplanted patients with persistent HPT

Cinacalcet reduced intact PTH from 176 to 136 pg/ml and reduced serum calcium. GFR remained stable. N=11
Effect of cinacalcet on iPTH and serum Ca and P in CKD patients with a **mean GFR of 23 ml/min**.
Serum PTH, calcium and phosphate before (month 0) and during treatment (months 1–3) with cinacalcet 30 mg/day.

Serum creatinine: 139±16 before and 148±16 µmol/l after cinacalcet.
Cinacalcet chloride is efficient and safe in renal transplant recipients with posttransplant hyperparathyroidism, N=9.
Effect of cinacalcet cessation in renal transplant recipients with persistent hyperparathyroidism

Creatinine, PTH, Ca and P before initiation (−12), after 1 year of cinacalcet (0) and, 2 weeks (0.5), 2 months(2) and 3 months (3) after cessation of cinacalcet. N=10
Effective control of persistent HPT with cinacalcet in renal allograft recipients N=12
Post-transplant bone disease
Prophylaxis / treatment 1

- Alphacalcidol or calcitriol 0.25 - 0.5 µg/day or 600 units of cholecalciferol/day
- Calcium intake of 1000 mg – post-menopausal women 1500 mg/day
- Treat persistent hyperparathyroidism, secondary as well as tertiary HPT
- Treat other causes of hypercalcemia
- Treat persistent hypophosphatemia
- Treat persistent hypomagnesemia
Post-transplant bone disease
Prophylaxis / treatment 2

- Tailor immunosuppression
- Use the least possible dose of steroids - consider alternate day therapy
- Use of "bone sparing steroids"?
- Use of calcitonin - nasal calcitonin?
- Avoid loop diuretics, if possible – use thiazides
- Restore gonadal/thyroid function
- Stop smoking
- Initiate exercise
Use of bisphosphonates might be considered:
1. as treatment of severe osteopenia and fractures in patients with a good and stable GFR > 50-60 ml/min
2. as would be the treatment of severe osteoporosis?
3. as prophylaxis - data are sparse!

Bisphosphonate should be avoided:
1. when GFR < 50 ml/min
2. in the presence of secondary and tertiary HPT.
3. in the case of hypovitaminosis D
4. to premenopausal women
Post-transplant bone disease
Prophylaxis / treatment 4
Calcimimetics

- Calcimimetics effectively reduce plasma PTH and calcium
- Calcimimetics increase plasma P
- Calcimimetics might not negatively affect kidney graft function
- Calcimimetics might not affect dosing or levels of CyA
- All observations are however based upon very small numbers