Bone Disease after Kidney Transplantation

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Clinical case

- 47 year old female FSGS
- DBD 2007
- eGFR 25 mls/min. Sirolimus, Azathioprine and prednisolone
- Smoker, low BMI, previous parathyroid surgery, premature menopause
- T score: -3.2 SD indicates osteoporosis
- Started Denosumab – stopped when eGFR<20

OSTEOPOROSIS: bone density is 2.5 standard deviations below a 30 year old adult
Talk outline

- How common are fractures and what are the outcomes of fractures after transplantation?

- Why are kidney transplant recipients at increased fracture risk?

- How can we prevent fractures?
  - Improving Bone Density
  - Vitamin D
  - Hyperparathyroidism
Incidence of hip fractures declining

- USRDS + Medicare data
- 69,740 KTRs
- Hip fracture incidence 3.8 /1000 patient years

45% reduction in hip fractures in 2010 compared to 1997

Sukumaran Nair S et al AJT 2014;14;943-51
Falling incidence of fractures – it's not just less steroids

- Single centre – 289 KTRs
- Better pre-transplant management of CKD-MBD
- More Bisphosphonate use

Perrin P et al. Transplantation 2017
Fracture risk and mortality in the England

16% dead within 1 year of hip fracture

- 21,769 KTRs between 2001 and 2013.
- Risk factors:
  - Age
  - Female
  - Diabetes
  - Fracture history
  - Ethnicity - white
Diabetics have significantly higher fracture risk

USRDS data. 11145 T1 Diabetics transplanted 2000-2006.

Talk outline

• How common are fractures and what are the outcomes of fractures after transplantation?

• **Why are kidney transplant recipients at increased fracture risk?**

• How can we prevent fractures?
  – Improving Bone Density
  – Vitamin D
  – Hyperparathyroidism
Fracture triangle in transplantation

FORCE

FALLS

FRACTURE

FALLS

FORCE

Bone Density

Bone Biopsy

Bone Quality

Bone Density

DXA

Bone Biopsy

Bone Quality
Increased bone fragility post-transplantation

**Pre-Transplant factors**
- Renal Osteodystrophy
- Dialysis vintage
- Gender
- Age
- Diabetes
- Ethnicity
- BMI/smoking/tobacco

**Post-Transplant factors**
- Steroids
- ↑PTH
- ↓Vit D

**Bone Fragility and Fracture Risk**
- Trabecular + Cortical bone loss
- Abnormal bone mineralisation and formation
Talk outline

• How common are fractures and what are the outcomes of fractures after transplantation?

• Why are kidney transplant recipients at increased fracture risk?

• How can we prevent fractures?
  – Improving Bone Density
  – Vitamin D
  – Hyperparathyroidism
Improving bone density

- Should we do DXA routinely post-transplantation?
- What is the impact of steroid minimisation?
- Do anti-osteoporotic therapies (bisphosphonates and denosumab) reduce fracture risk?
DXA predicts fracture risk post transplantation

Fracture risk

- Osteoporosis
- Osteopenia
- Normal BMD

Bone density remains normal in most KTRs

DXA changed management in only 19% of patients

Naylor KI et al Transplantation 2014
Improving bone density

- Should we do DXA routinely post-transplantation
- Steroid minimisation
- Anti-osteoporotic therapy – bisphosphonates and denosumab
Steroids reduce bone turnover and formation and increase bone loss.

Bone Turnover

Bone Loss

Evenepoel P et al. Kid Int 2017
Early steroid withdrawal minimises bone loss

Iyer S P et al. 2014, JASN
Late steroid withdrawal improves BMD

BMD change

Early steroid withdrawal and reduced fracture risk

Steroids

31% reduction in fracture risk

Steroid-free at discharge

Improving bone density

- Should we do DXA routinely post-transplantation
- Steroid minimisation
- Anti-osteooporotic therapy – bisphosphonates and denosumab
Targeting osteoclastic activity

The problem with osteoporosis therapy

- Bisphosphonates cleared by the kidney

- 50% of bisphosphonate dose deposits in skeleton and may be there for 10 years!

- Both bisphosphonates and denosumab can potentially exacerbate adynamic bone disease

- Evidence for denosumab and bisphosphonates reducing fractures very limited when GFR<30mls/min
Pamidronate reduces BMD loss post-transplant

All subjects received calcium and colecalciferol

Fracture rate 3.3% in treatment group vs 6.2% in control

Studies of bisphosphonophosphonates in KTx

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No evidence that bisphosphonates reduce fractures

Effect on bone density marginal in current era – less steroids, better pre-transplant PTH
Denosumab improves bone density in KTRs

- Higher risk of urinary sepsis
- Hypocalcaemia
- No fracture data

Bonani M et al. AJT 2016
Talk outline

• How common are fractures and what are the outcomes of fractures after transplantation?

• Why are kidney transplant recipients at increased fracture risk?

• How can we prevent fractures?
  – Improving Bone Density
  – Vitamin D
  – Hyperparathyroidism
Does native vitamin D supplementation improve graft and bone outcomes?

VITA-D study: outcome of a 1-year randomized controlled trial to evaluate vitamin D3 supplementation in vitamin D deficient renal transplant patients
Ursula Thiem et al.
Treatment of vitamin D deficiency in KTRs did not improve the short-term post-transplant outcome but may even have adverse effects on renal allograft function. The data suggest that vitamin D should not be supplemented in the first year after kidney transplantation.
VITamine D supplementation in renAL transplant recipients (VITALE): a prospective, multicentre, double-blind, randomized trial of vitamin D estimating the benefit and safety of vitamin D₃ treatment at a dose of 100,000 UI compared with a dose of 12,000 UI in renal transplant recipients: study protocol for a double-blind, randomized, controlled trial

Marie Courbebaisse, Corinne Alberti, Sandra Colas, Dominique Prié, Jean-Claude Souberbielle, Jean-Marc Treluyer, and Eric Thervet
Talk outline

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Post-transplant hyperparathyroidism

- 59 year old spina bifida
- HLAi live related Tx in 2007.
- Tacrolimus + Prednisolone
Hyperparathyroidism persists post transplant

- PTH normal in 20-30% at 1 year
- Hypercalcaemia occurs in 30-50% of high PTH group

Wolf M et al Transplantation 2015
High PTH has a catabolic effect on cortical bone

Steroid withdrawn at day 3

Iyer S P et all. 2014. JASN
Persistent hyperparathyroidism is a risk factor for fractures


PTH>130ng/l

PTH<130ng/l

P < 0.001
Both active vitamin D and paracalcitol suppress PTH post-transplant.

Cruzado JM et al. Kidney Reports 2018
Cinacalcet corrects mineral abnormalities in hyperparathyroidism

- RCT - 114 KTRs
- Hypercalcaemic hyperparathyroidism
- No effect on bone density

Evenpoel P et al. AJT 2014; 14: 2545–2555a
Fractures – it's not all about bone

- Bone Fragility
- Falls
- Fraility

Factors:
- Postural hypotension
- Drugs
- Lifestyle
- Nutrition
- Exercise
Conclusions

• How common are fractures are they important?
• About 10/1000 patient years - high mortality in those with hip fracture

• Should everyone get at DXA during the 1\textsuperscript{st} year post transplant?
• Only those with eGFR>30 and at high risk of fracture – age, sex, falls risk, diabetic, previous fractures, significant bone disease on dialysis

• How should post-transplant osteoporosis be treated?
  – Bisphosphonates in those with an GFR>30mls/min/1.73m\textsuperscript{2}
  – Denosumab if eGFR bewteen 20-30mls/min/1.73m\textsuperscript{2}
Conclusions

• Should we look for and treat native vitamin D deficiency in everybody?
• Don’t know – but probably safe as long as avoid hypercalcaemia

• Which patients with persistent hyperparathyroidism post transplant should be treated?
  – Hypercalcaemia (calcium >2.8mmol/l)
  – Likely high bone turnover – high bone alkaline phosphatase
  – Significant loss in bone density on DXA – i.e. osteopenia or osteoporosis
  – Fractures

• How should hyperparathyroidism be treated?
• Active vitamin D or cinacalcet for those with hypercalcaemia