Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Bone Disease after Kidney Transplantation

BTS March 2018

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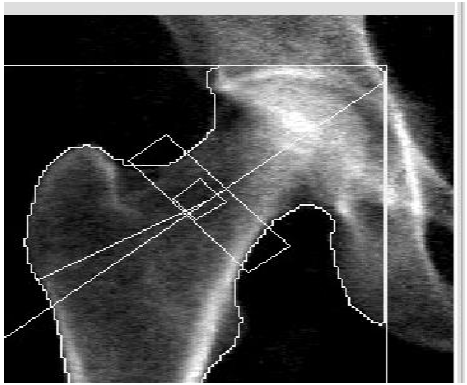
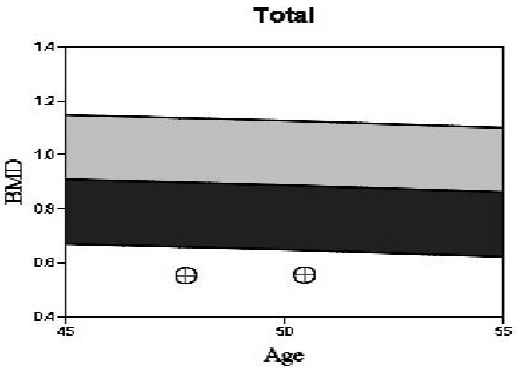
SheffieldKidneyInstitute

Clinical case

- 47 year old female FSGS
- DBD 2007
- eGFR 25mls/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

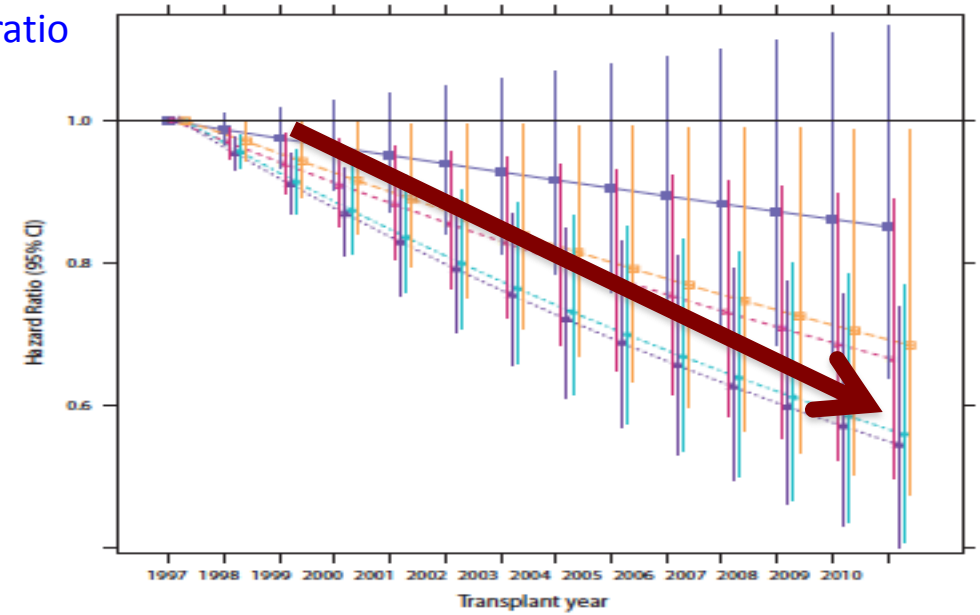
- How common are fractures and what are the outcomes of fractures after transplantation?

- 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

Hazard ratio

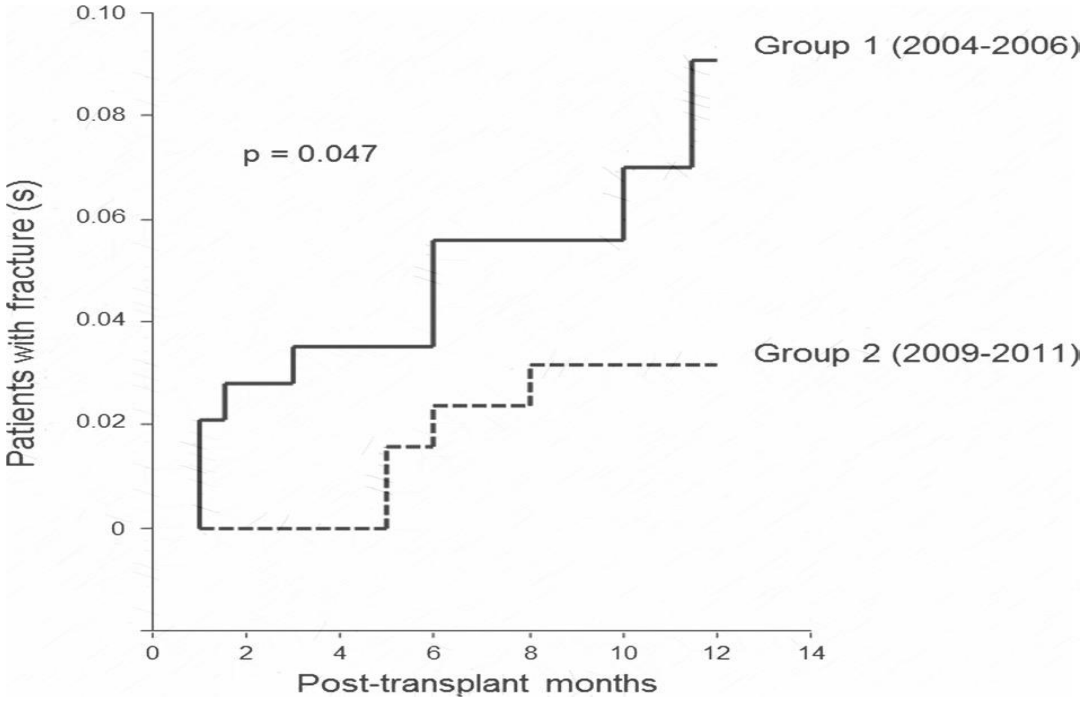


- USRDS +Medicare data
- 69,740 KTRs
- **Hip fracture incidence 3.8 /1000 patient years**

45% reduction in hip fractures in 2010 compared to 1997

Sukumaran Nair S et al AJT 2014;14;943-51

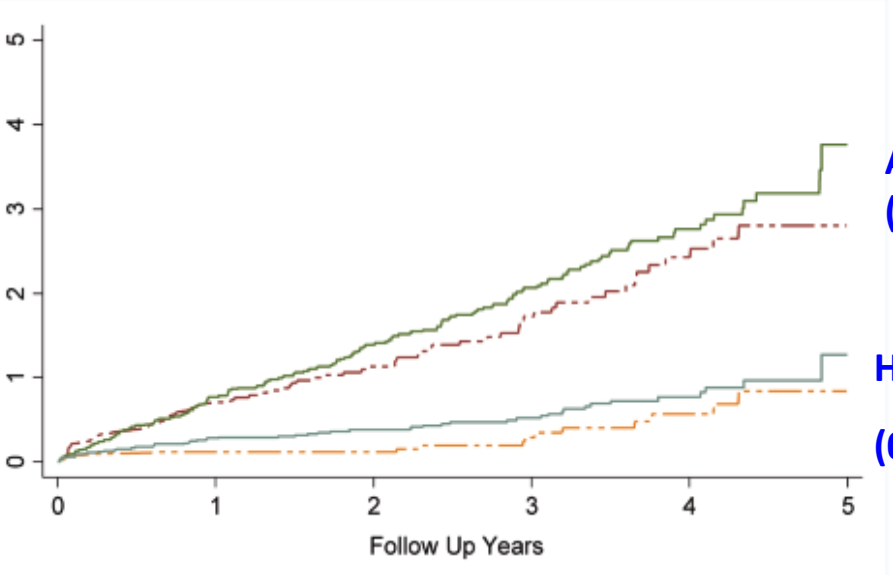
Falling incidence of fractures – its not just less steroids



- 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



All fractures (3.8%)

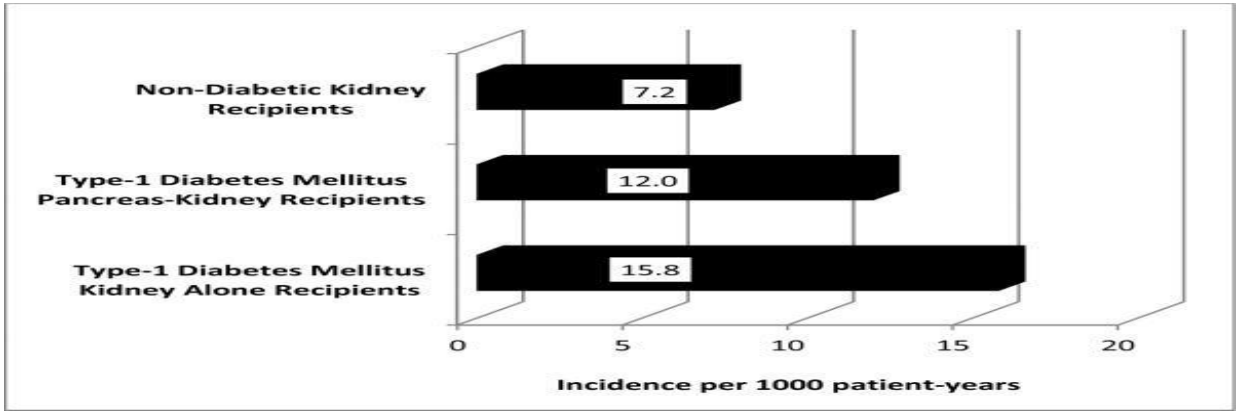
Hip fractures (0.8%)

- 21,769 KTRs between 2001 and 2013.
- **Risk factors:**
  - **Age**
  - **Female**
  - **Diabetes**
  - **Fracture history**
  - **Ethnicity - white**

16% dead within 1 year of hip fracture

Ferro CJ et al Clin Transp 2015
Arnold J et al. Exp and Clin Transp 2017

Diabetics have significantly higher fracture risk



USRDS data. 11145 T1 Diabetics transplanted 2000-2006.

Nikkel LE et al. Kidney Int. 2013; 83(3):471-8

Talk outline

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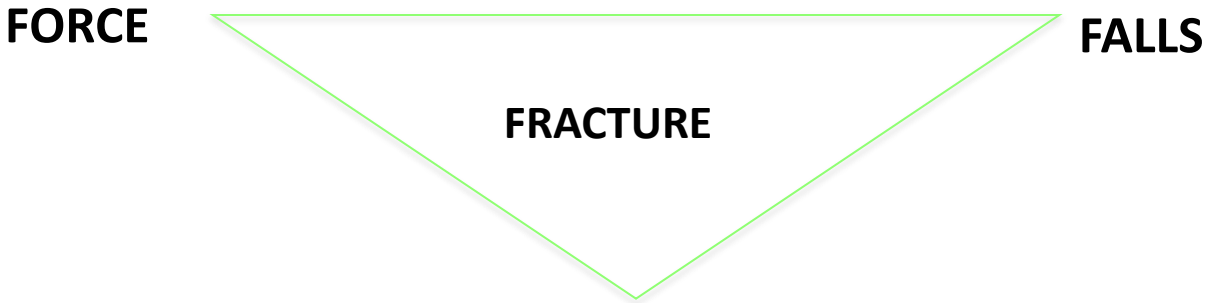
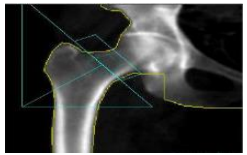
- **Why are kidney transplant recipients at increased fracture risk?**

- How can we prevent fractures?
  - Improving Bone Density
  - Vitamin D
  - Hyperparathyroidism

Fracture triangle in transplantation

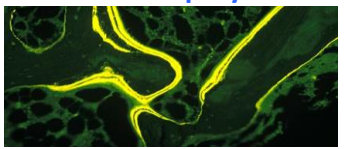


DXA



BONE FRAGILITY

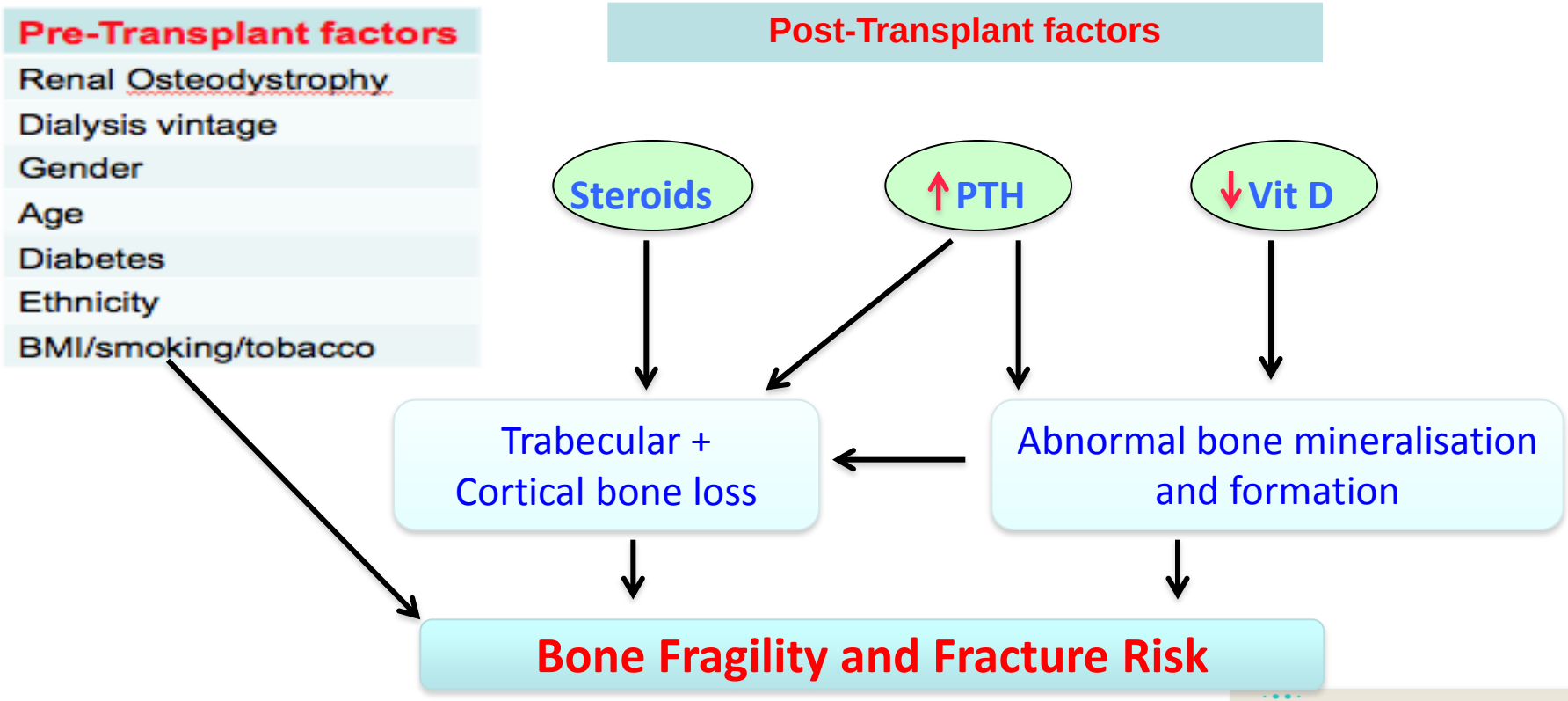
Bone Biopsy



Bone Density

Bone Quality

Increased bone fragility post-transplantation



Talk outline

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

- Why are kidney transplant recipients at increased fracture risk?

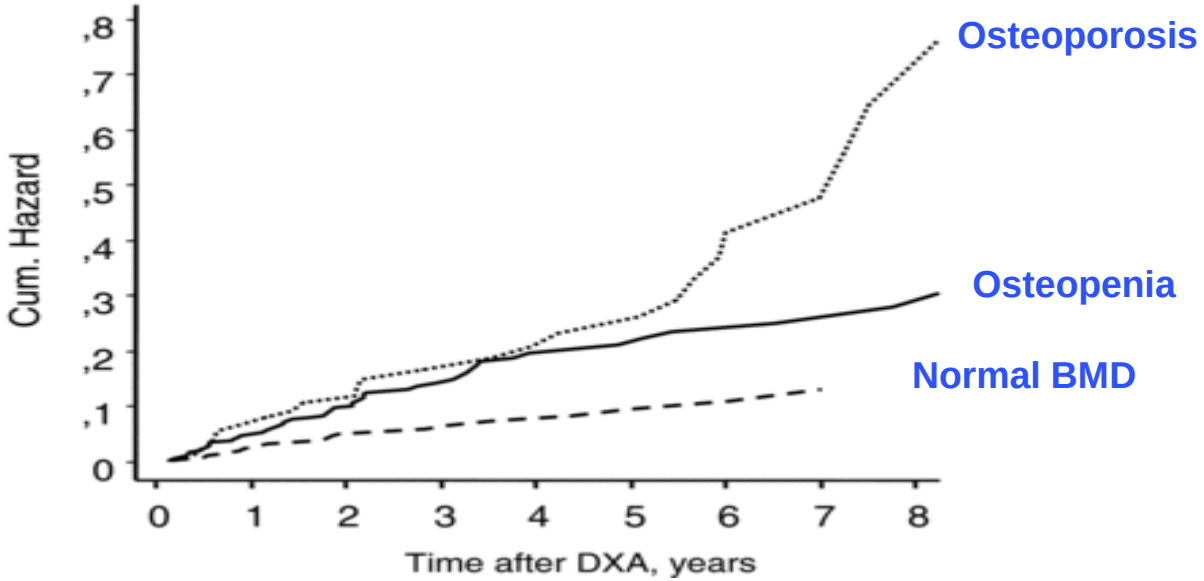
- **How can we prevent fractures?**
  - **Improving Bone Density**
  - Vitamin D
  - Hyperparathyroidism

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?

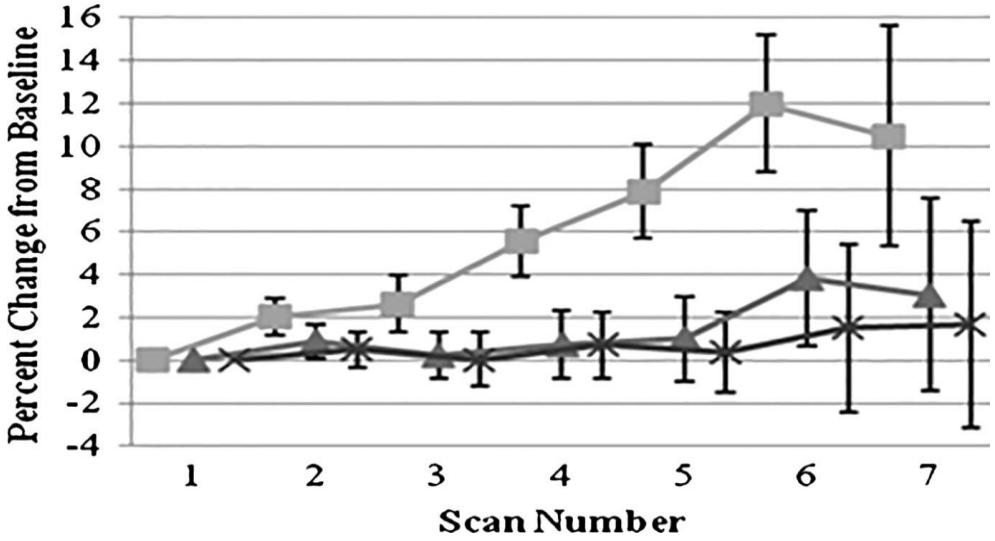
DXA predicts fracture risk post transplantation

Fracture risk



Akaberi S et al. American Journal of Transplantation2008

Bone density remains normal in most KTRs



Lumbar spine

Hip

Femoral neck

DXA changed management in only 19% of patients

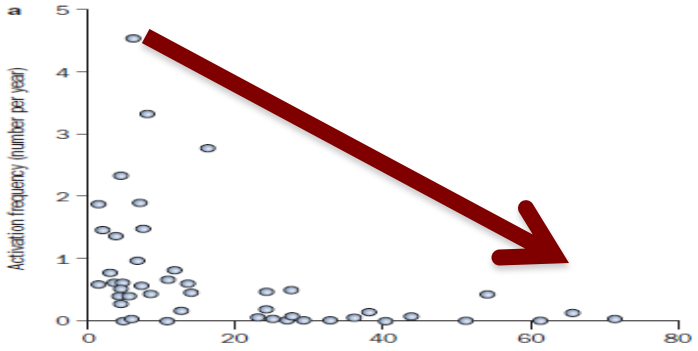
Naylor KI et al Transplantation 2014

Improving bone density

- Should we do DXA routinely post-transplantation
- **Steroid minimisation**
- Anti-osteoporotic therapy – bisphosphonates and denosumab

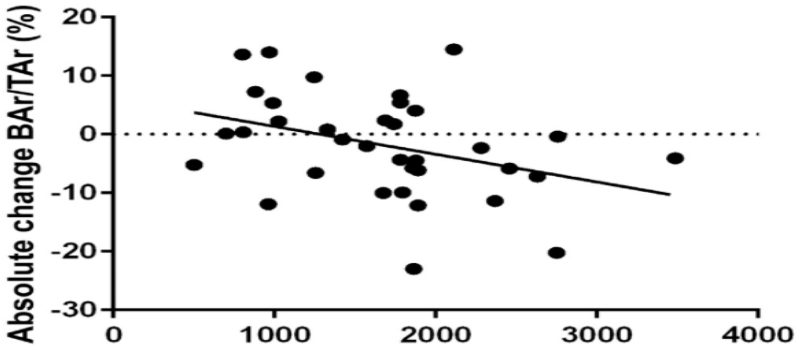
Steroids reduce bone turnover and formation and increase bone loss

Bone Turnover



Steroid dose

Bone Loss



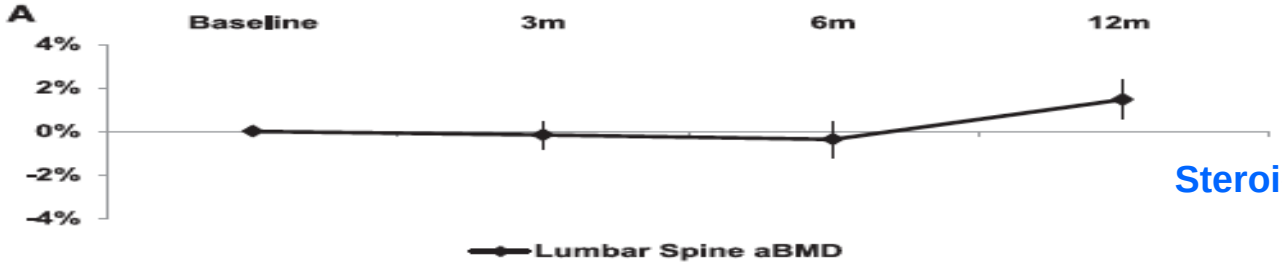
Steroid dose

Evenepoel P et el Kid Int 2017

Monier-Faugere MC et al. J Am Soc Nephrol 11: 1093–1099, 2000

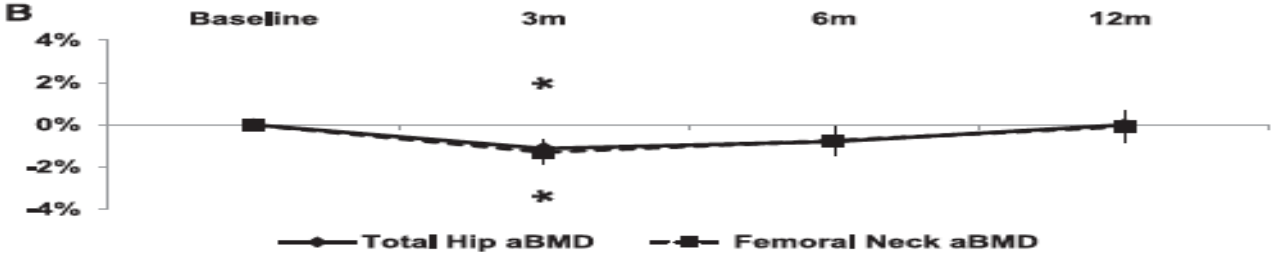
Early steroid withdrawal minimises bone loss

Lumbar spine



Steroid withdrawn at day 3

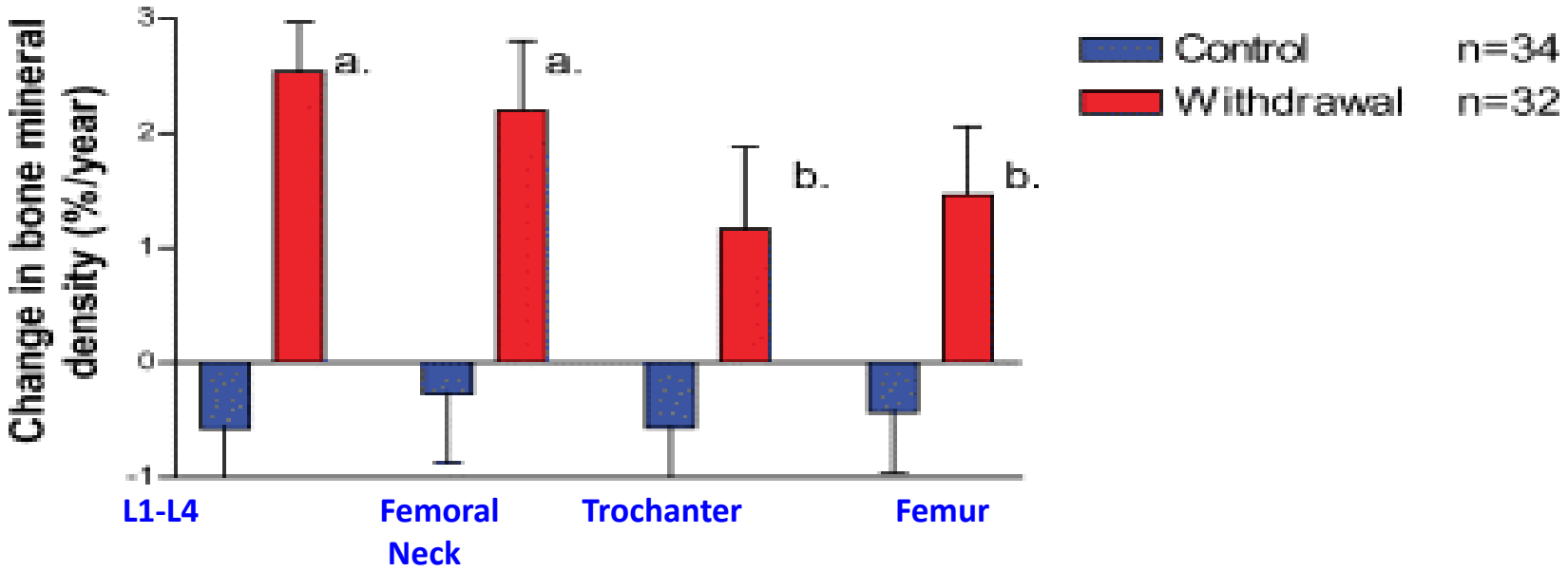
Hip



Iyer S P et all. 2014. JASN

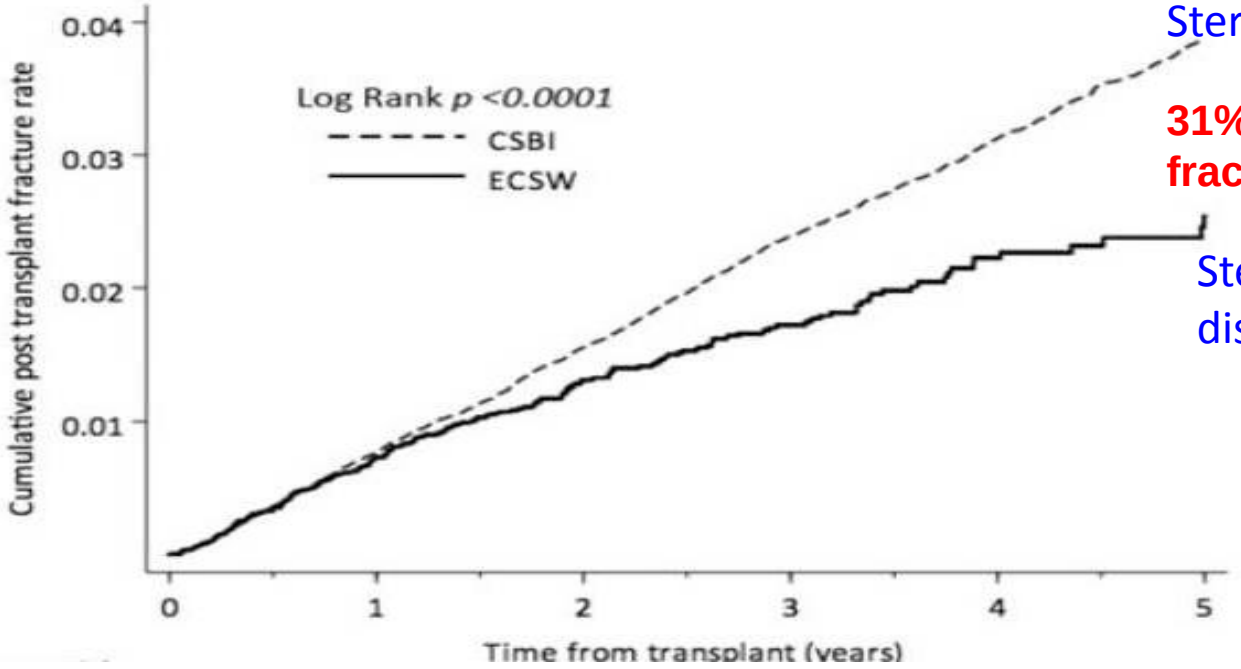
Late steroid withdrawal improves BMD

BMD change



Farmer CKT et al, Am J Trans. *2006;* 6: 2929–2936

Early steroid withdrawal and reduced fracture risk



Steroids

31% reduction in fracture risk

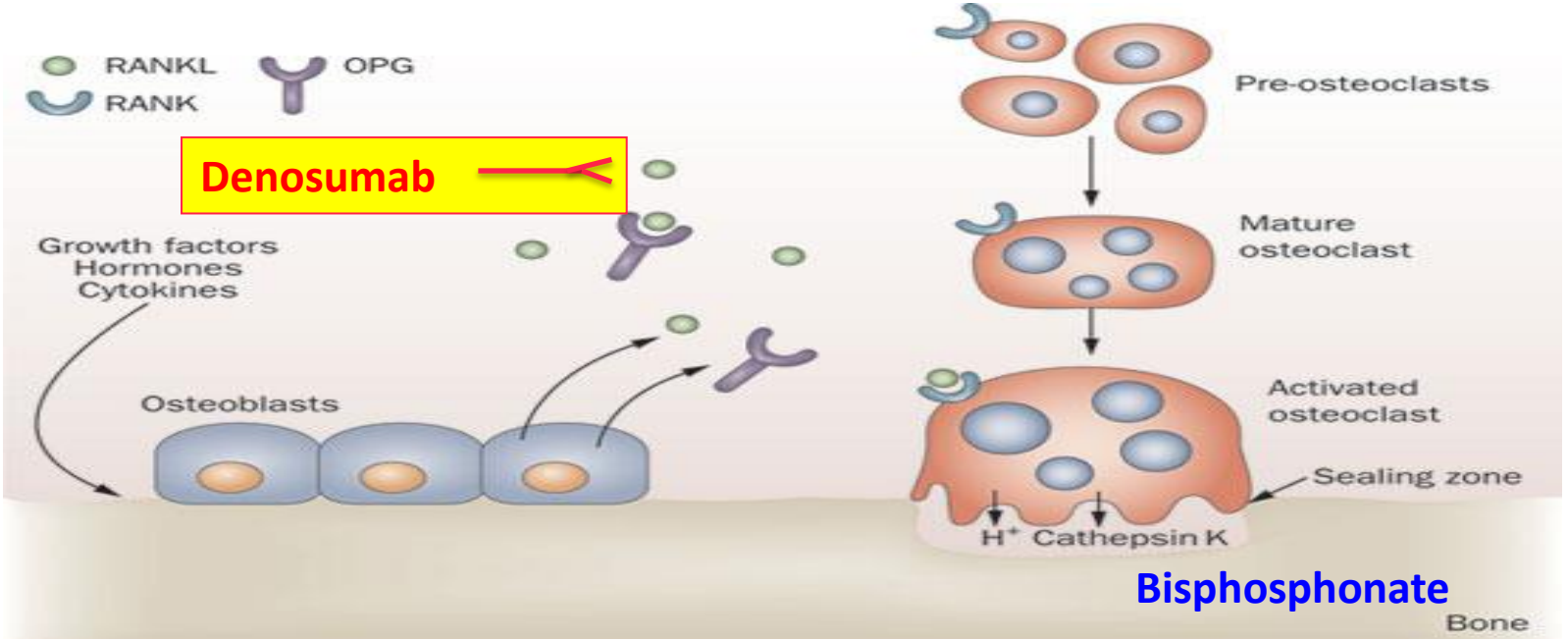
Steroid-free at discharge

Nikkel LE et al, Am J Trans. *2012; 12: 649–659*

Improving bone density

- Should we do DXA routinely post-transplantation
- Steroid minimisation
- **Anti-osteoporotic therapy – bisphosphonates and denosumab**

Targeting osteoclastic activity

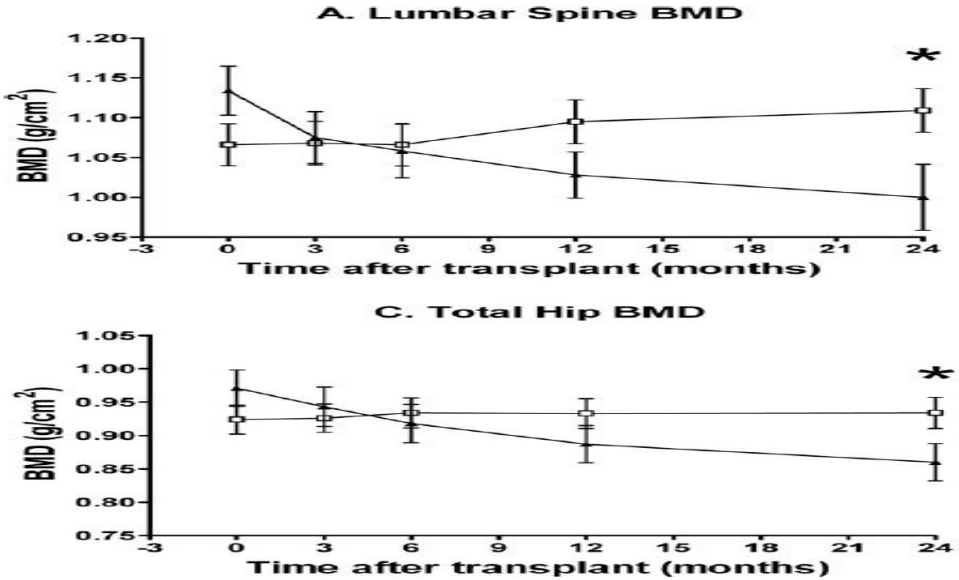


Lewiecki, E. M. (2011) *Nat. Rev. Rheumatol.*

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

Walsh SB et al. Am J Kid Dis Vol 53, No 5 (May), 2006: pp 856-865

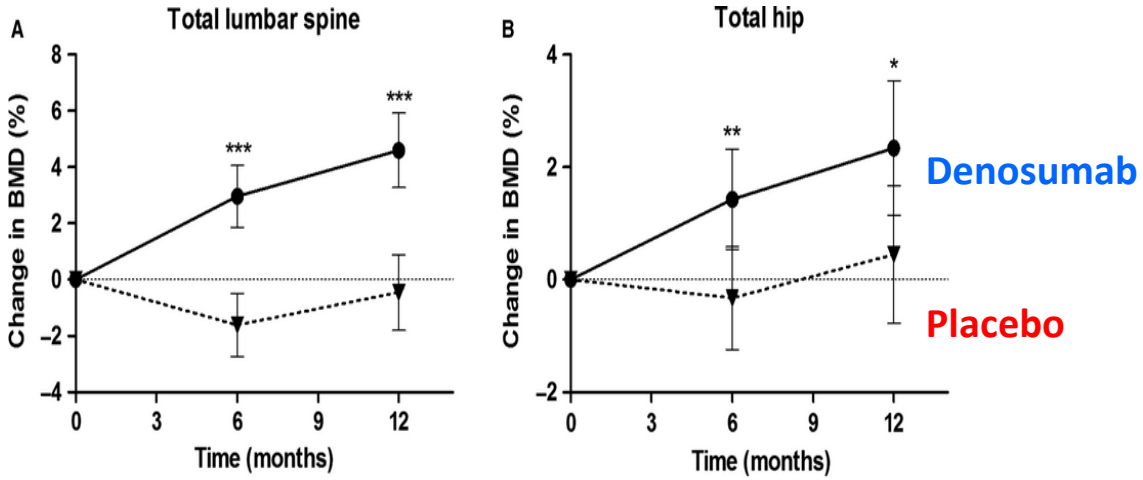
Studies of bisphosphonates in KTx

Study	Pt No	Steroids	Agent	Duration	Endpoint	Benefit
Kovac et al	12	Yes	**Alendronate**	6	**BMD**	Nil
Giannini et al	40	Yes	**Alendronate**	12	**BMD**	Nil
Grotz et al.	80	Yes	**Ibandronate**	12	**BMD**	Yes
Jeffery et al.	117	Yes	**Alendronate**	12	**BMD**	Nil
Fan et al	26	?	**Pamidronate**	48	**BMD**	Yes
Haas et al	20	Yes	**Zolendronate**	6	**BMD**	Yes
Coco et al	72	Yes	**Pamidronate**	12	**BMD**	Yes
Schwarz et						
Walsh et al						
Torregrosa						
Torregrosa						
Smerud et al						
Coco et al						

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.

VITamin D supplementation in renAL transplant recipients (VITALE): a prospective, multicentre, double-blind, randomized trial of vitamin D estimating the benefit and safety of vitamin D_3 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

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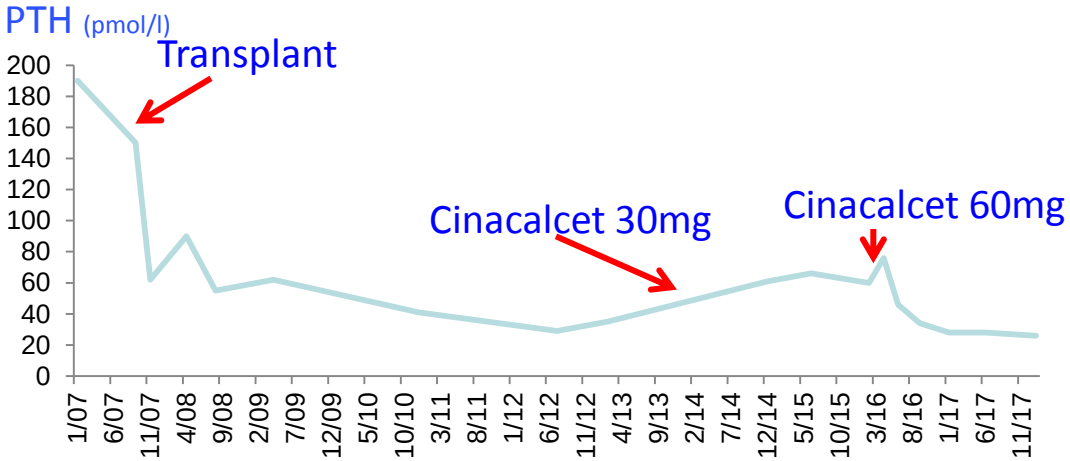
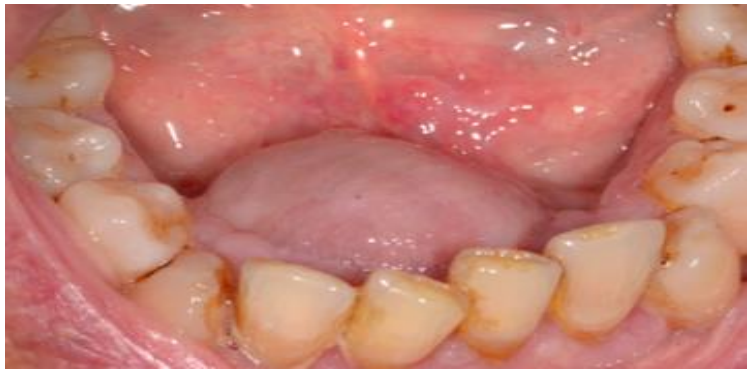
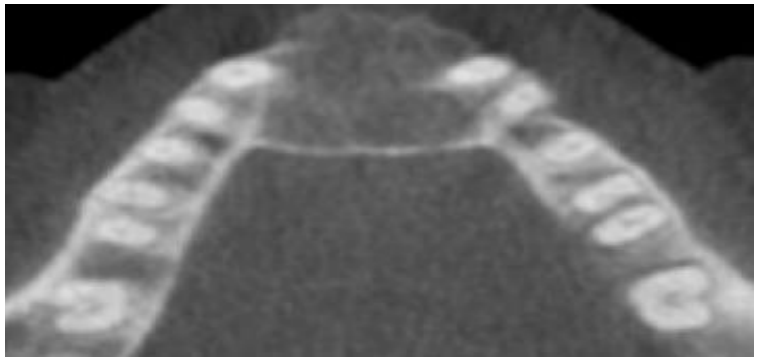
  - Improving Bone Density
  - Vitamin D
  - **Hyperparathyroidism**

Post-transplant hyperparathyroidism

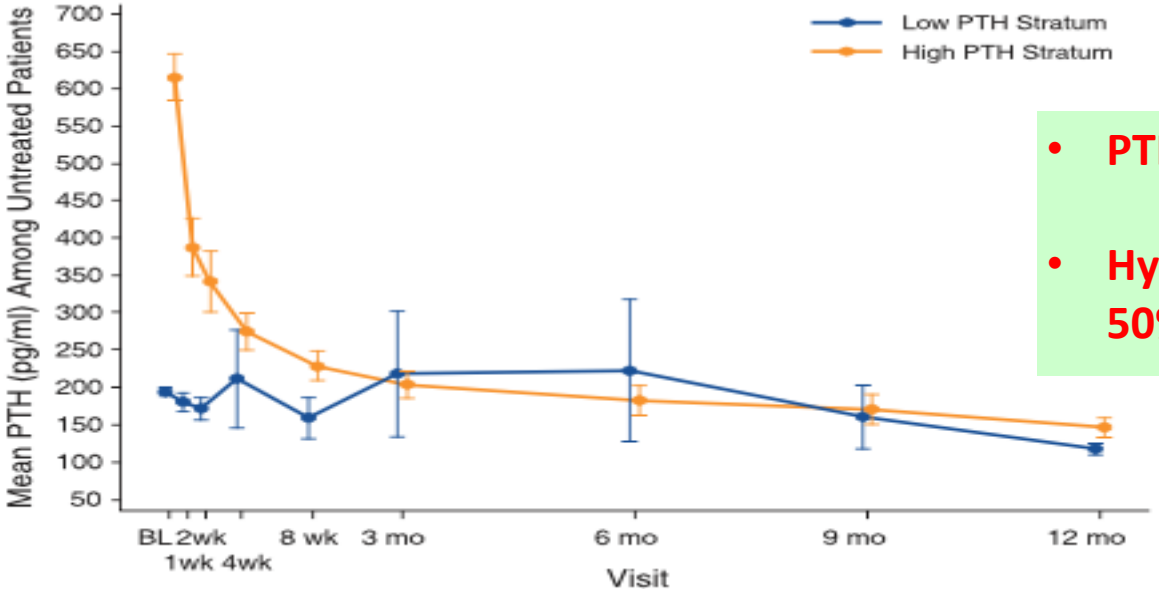






- 59 year old spina bifida
- HLAi live related Tx in 2007.
- Tacrolimus+ Prednisolone

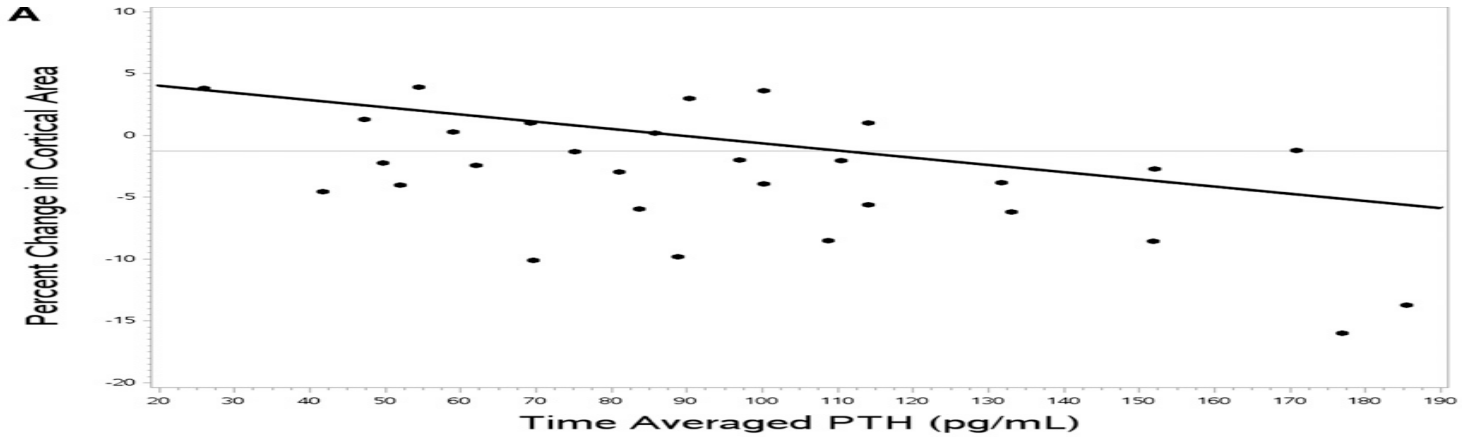
Hyperparathyroidism persists post transplant



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

Wolf M et al Transplantation 2015

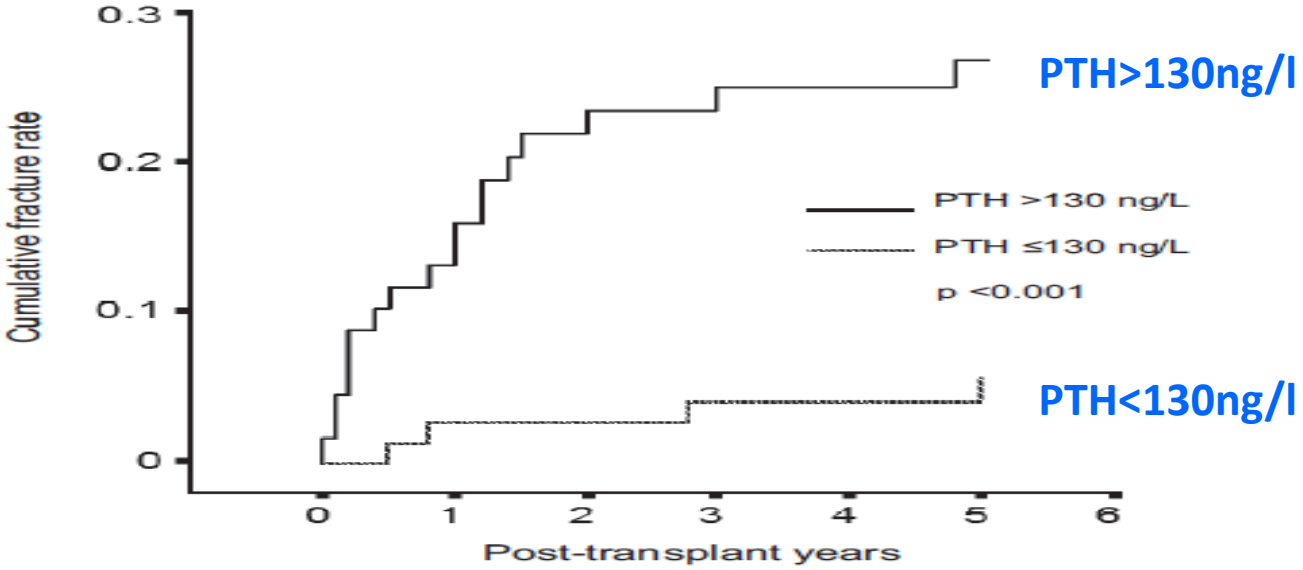
High PTH has a catabolic effect on cortical bone



Steroid withdrawn at day 3

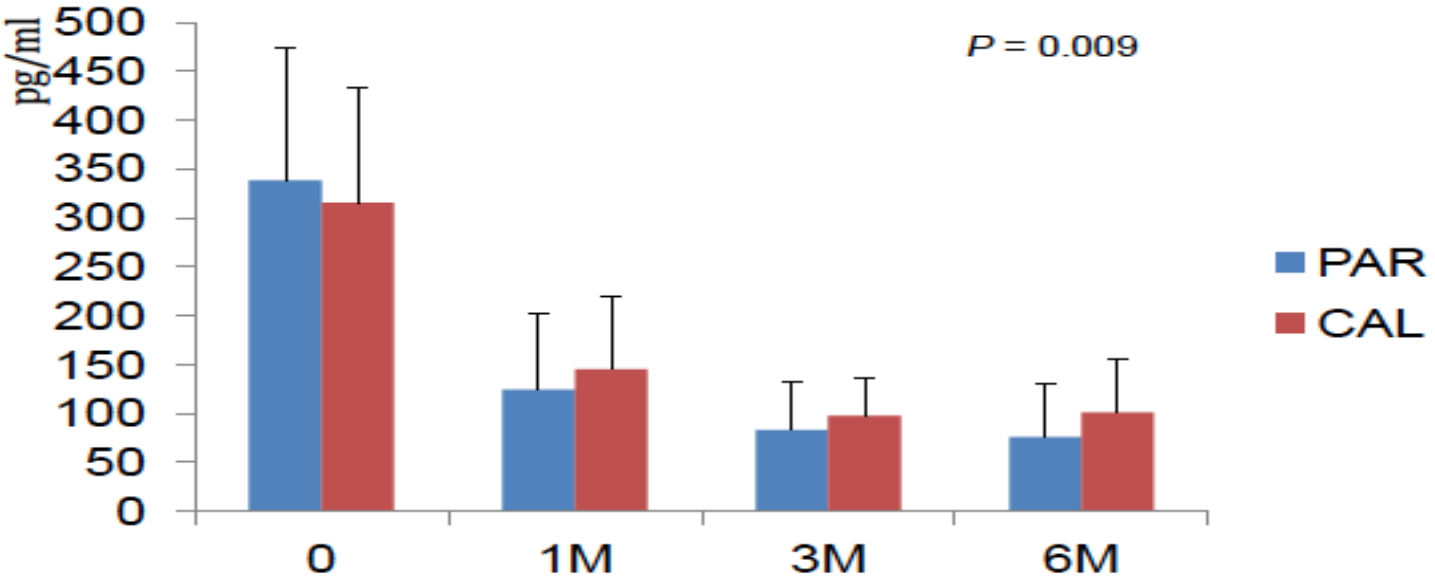
Iyer S P et all. 2014. JASN

Persistent hyperparathyroidism is a risk factor for fractures



Perrin P et al. Am J Trans. 2013; 13; 2653-2663

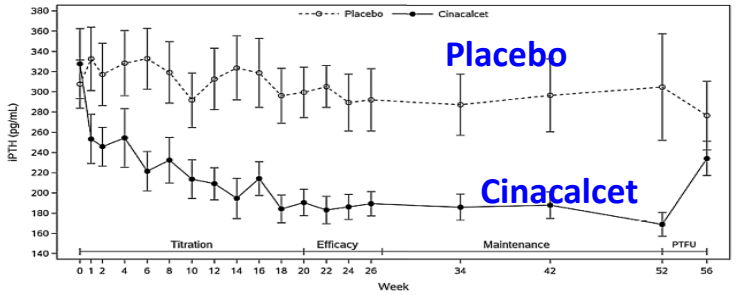
Both active vitamin D and paracalcitol suppress PTH post-transplant



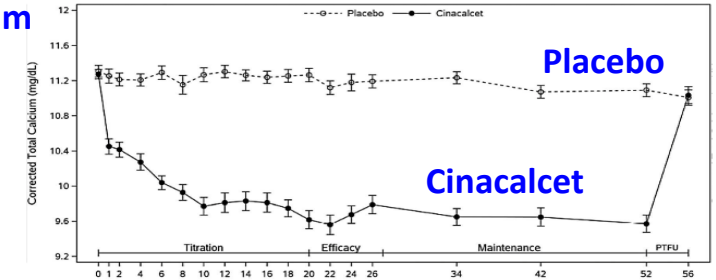
Cruzado JM et el KI Reports 2018

Cinacalcet corrects mineral abnormalities in hyperparathyroidism

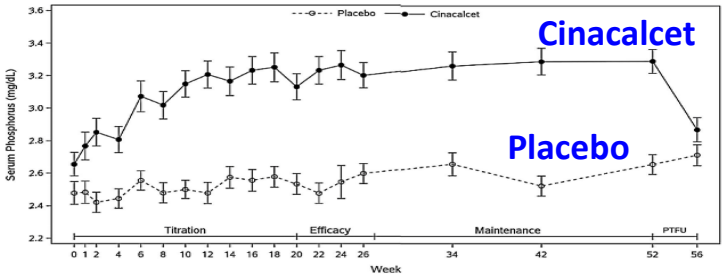
PTH



Calcium



Phosphorus



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

Evenpoel P et al. AJT 2014; 14: 2545–2555a

Fractures – its not all about bone

Postural hypotension drugs

Falls

Bone Fragility

Fraility

FRACTURES

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 1st 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^2**
  - **Denosumab if eGFR bewteen 20-30mls/min/1.73m^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 done density on DXA – i.e. osteopenia or osteoporosis**
  - **Fractures**
- How should hyperparathyroidism be treated?
- **Active vitamin D or cinacalcet for those with hypercalcaemia**