Organ Transplantation and Osteoporosis

Interdisciplinary Symposium on Osteoporosis

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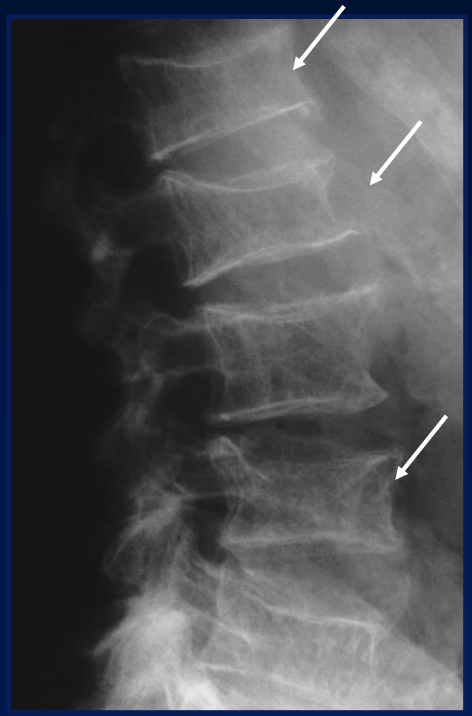
Disclosures

Research Support:

- Novartis Pharmaceuticals
- Radius Health

A Case of Post-Transplant Osteoporosis

- 49 year old man
- History
  - Heart transplant for viral cardiomyopathy
  - Severe back pain at 2 months
  - Several recurrences over next 6 months
- Physical Exam
  - 6’ 2” before transplant
  - 5’ 10” after transplant
  - Marked kyphosis
- Spine x-rays - 7 vertebral fractures

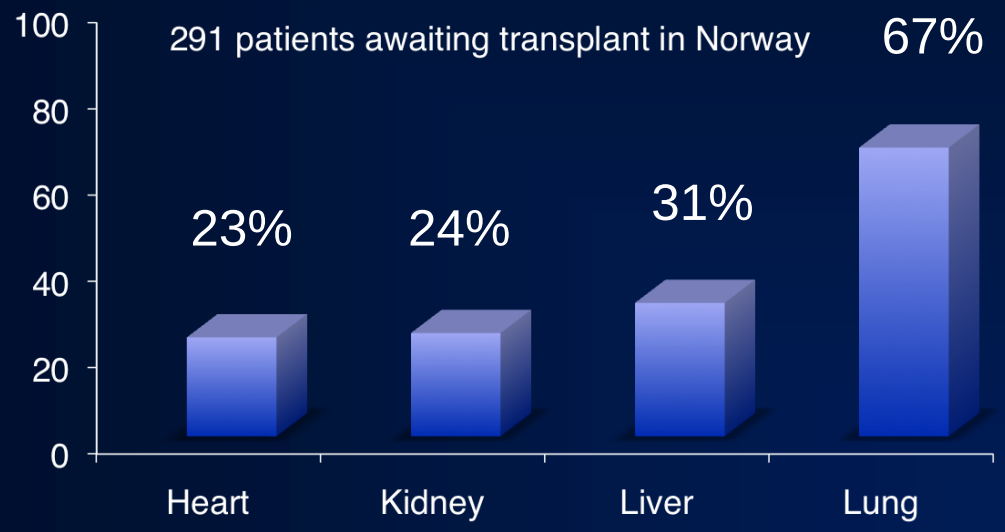


Outline

- Skeletal Disease in Patients Awaiting Transplantation
- Epidemiology and Pathogenesis of Osteoporosis After Transplant
- Bone Loss After Transplantation: Clinical Trials
- Prevention of Post-Transplant Fractures
- Management of Bone Disease Post-Transplant
- Management of Bone Disease After Kidney Transplant

Skeletal Disease in Patients Awaiting Transplantation

Prevalence of Osteoporosis by DXA in Transplant Candidates



Adapted from Hartmann, Clin Tranaspl 2010

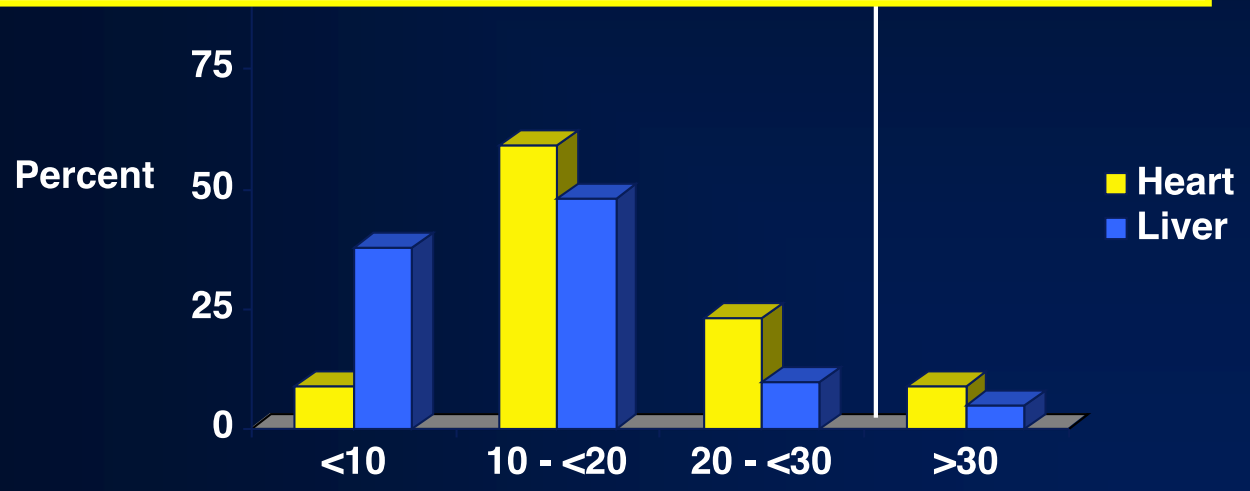
Causes of Low BMD in Candidates AWAITING Transplantation

- Older age
- Postmenopausal
- Tobacco
- Alcohol
- Drugs: Loop diuretics, heparin, steroids
- Physical inactivity
- Diabetes [1]
- Low calcium intake
- Vitamin D deficiency [2]

1. Rakel et al., J Bone Miner Res. 2007
2. Stein et al., Clin Transpl. 2009

Vitamin D Deficiency in Recent Transplant Recipients

Serum levels of free 25OHD may not be as low.



Stein et al., Clin Transpl. 2009

Causes of Low BMD in Candidates <u>AWAITING</u> Transplantation

- Older age
- Postmenopausal
- Tobacco
- Alcohol
- Drugs: Loop diuretics, heparin, steroids
- Physical inactivity
- Diabetes [1]
- Low calcium intake
- Vitamin D deficiency [2]
- **End-stage liver, kidney, lung and heart disease**

1. Rakel et al., J Bone Miner Res. 2007
2. Stein et al., Clin Transpl. 2009

Risk Factors for Low Bone Mass and Fractures in Patients with Heart Failure

- Chronic kidney disease
- Loop diuretics
- Heparin
- Low physical activity
- Vitamin D deficiency
- Secondary hyperparathyroidism
- Hypogonadism

Majumdar et al. JCEM 2012, Lyons et al, Circ Heart Fail 2011, Mazziotti et al. Eur J Endocrinol 2011

Risk Factors for Low Bone Mass and Fractures in Patients with Chronic Lung Disease

- Glucocorticoids
- Hypoxemia, Acidosis
- Cachexia
- Tobacco
- Cystic Fibrosis
  - Low peak bone mass
  - Pancreatic insufficiency
  - Calcium and D malabsorption
  - Hypogonadism

Graat-Verboon et al, Bone 2012. Romme et al. Exp Rev Respir Med 2013. Paccou et al, Calcif Tiss Int 2010. Lakey Clin Transplant 2011. Jastrzebski Eur J Med Res 2010.

Risk Factors for Low Bone Mass and Fractures in Patients with End-Stage Liver Disease

- HCV infection
- Alcohol use
- Hemochromatosis
- Cirrhosis +/- encephalopathy
- Primary Biliary Cirrhosis
  - Chronic cholestasis
  - Low bone turnover
- Vitamin D deficiency

Lo Re et al, Hepatology 2012. Webaux et al, Joint, Bone Spine 2011. Santori et al, J Endocrinol Invest 2008; Tsai et al, J Hepatol, 2013.

Risk Factors for Low Bone Mass and Fractures in Patients with End Stage Kidney Disease

- CKD-MBD: complex disturbances in bone
  - Disordered calcium and phosphate metabolism
  - Calcitriol deficiency
  - Secondary hyperparathyroidism
- Type 1 DM, Diabetic nephropathy
- Hypogonadism secondary to uremia
- Medications: Loop diuretics, Glucocorticoids, Cyclosporine
- Duration of dialysis
- Peripheral vascular disease
- Prior kidney transplant

Alem et al, Kidney Int, 2000. Nair et al., CJASN 2013.

Skeletal Disease in Organ Transplant Recipients

Incidence of Bone Loss and Fracture Immediately After Transplantation

Organ	Bone Loss During 1st Year		Fracture Incidence	
Kidney	Spine:	**4 - 9%**	Vertebral:	**3 - 10%**
Liver	Spine: Hip:	**0 - 24%** **0 - 4%**	Vertebral:	**24 - 65%**
Lung	Spine: Hip:	**1 - 5%** **2 - 5%**	All types:	**18 - 37%**

More recent studies show lower rates of bone loss and fracture.

Cohen, 2003; Maalouf, 2005; Stein, 2007; Ebeling, 2009; Kulak, 2010; Hamdy 2007; Malluche 2010; Huang & Sprague 2009

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PREVALENCE of Osteoporosis in LONG-TERM Transplant Survivors

Organ	Osteoporosis by BMD Criteria*	Fracture Prevalence
Kidney	**11 - 56%**	**3 - 43%**
Heart	**25 - 50%**	**12 - 35%**
Liver	**16 - 46%**	**29 - 47%**
Lung	**57 - 73%**	**22 - 42%**

* T ≤ -2.5 or Z ≤ -2.0

Cohen, 2003; Maalouf, 2005, Stein, 2007; Ebeling, 2009; Kulak, 2010; Hamdy 2007; Malluche 2010; Huang & Sprague 2009 ; Butin, 2017

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Pathogenesis of Skeletal Disease in Transplant Recipients

Immunosuppressive Therapy

- **Glucocorticoids**
- Calcineurin Inhibitors
  - Cyclosporine A
  - Tacrolimus (FK506)

Westenfeld, Nephrol Dial Transplant 2011

Glucocorticoids Uncouple Bone Remodeling

Most common secondary cause of osteoporosis

<u>Profoundly</u> decrease bone formation

- Decrease osteoblast number, function and survival

Slightly increase bone resorption

- Increase osteoclast number, maturation
  - Increase osteoblast production of RANK Ligand
  - Decrease osteoblast production of OPG

Osteocyte apoptosis, directly decrease bone strength

Other Detrimental Skeletal Effects of Glucocorticoids

- **DECREASE**
  - IGF-1 synthesis
  - Gonadal steroid production
  - Intestinal calcium absorption
  - Muscle mass and strength
- **INCREASE**
  - Urinary calcium excretion
  - ? PTH secretion

Calcineurin Inhibitors (CI)

Inhibit activation of NFAT, a key regulator of T cell function

- NFAT ALSO key transcription factor for osteoblasts and osteoclasts

In vitro

- INHIBIT osteoclast and osteoblast formation
- Expected CIs to cause low bone turnover

In animal studies

- Rapid, severe cancellous bone loss
- Markedly increased bone resorption and formation
- Tacrolimus (FK506) - similar effects but probably less severe
- Prevented by antiresorptive drugs - estrogen, bisphosphonates

Epstein, J Bone Miner Res. 1996
Buchinsky Endocrinol 1996 Sass, Bone 1997
Schlossberg, Endocrinol 1989
Cvetkovic, Transplantation 1994

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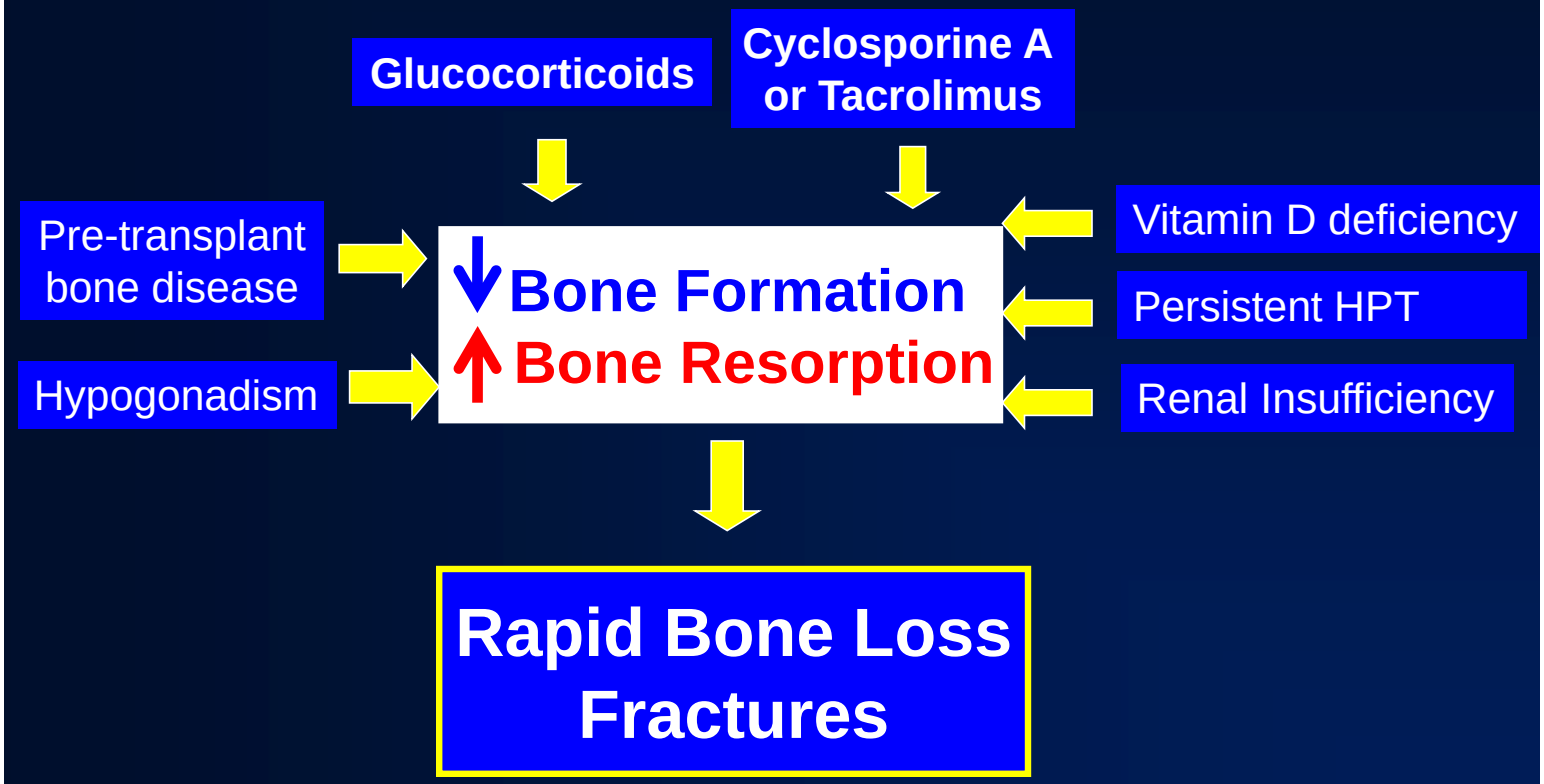
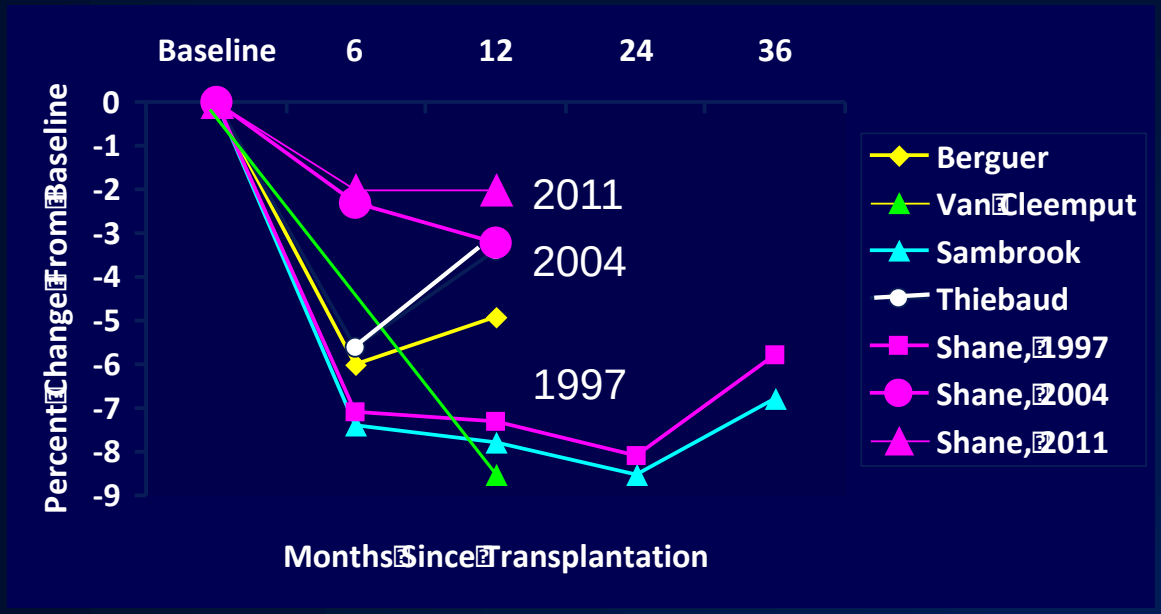
Pathogenesis of Transplantation Osteoporosis



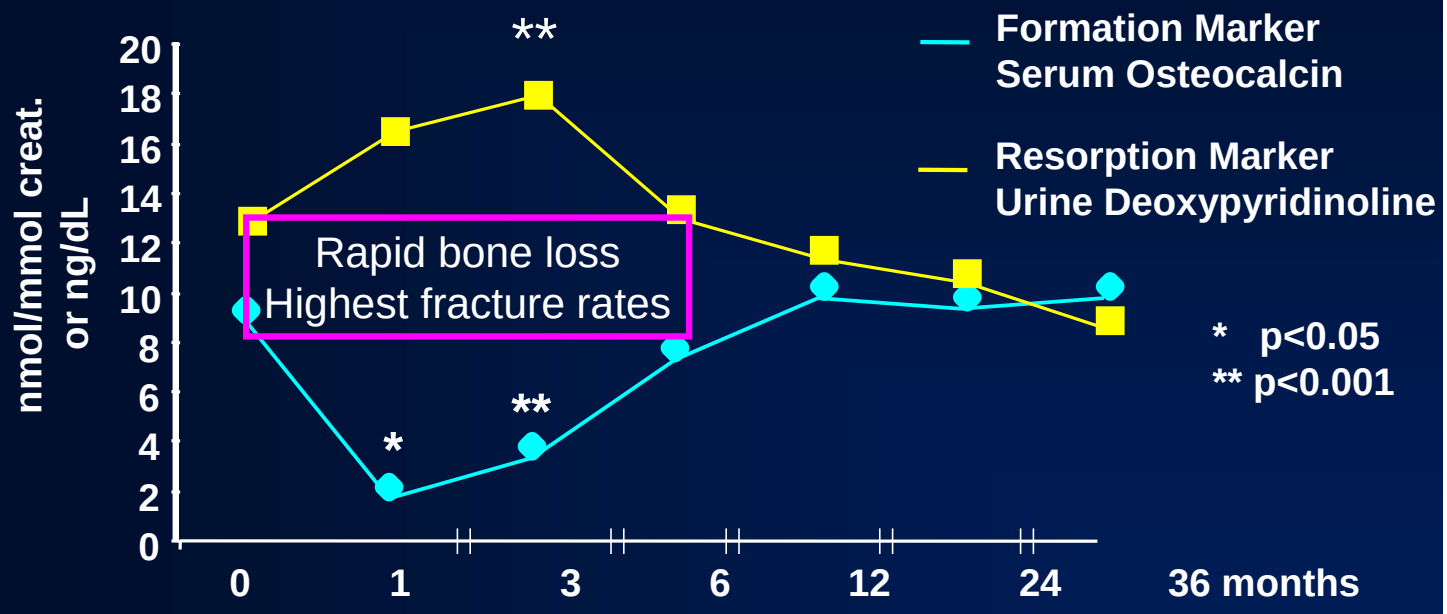
Adapted from Compston JE. Liver Transpl 2003

Natural History of Bone Loss After Transplantation

Lumbar Spine Bone Loss After Heart Transplantation From 1990s - 2011

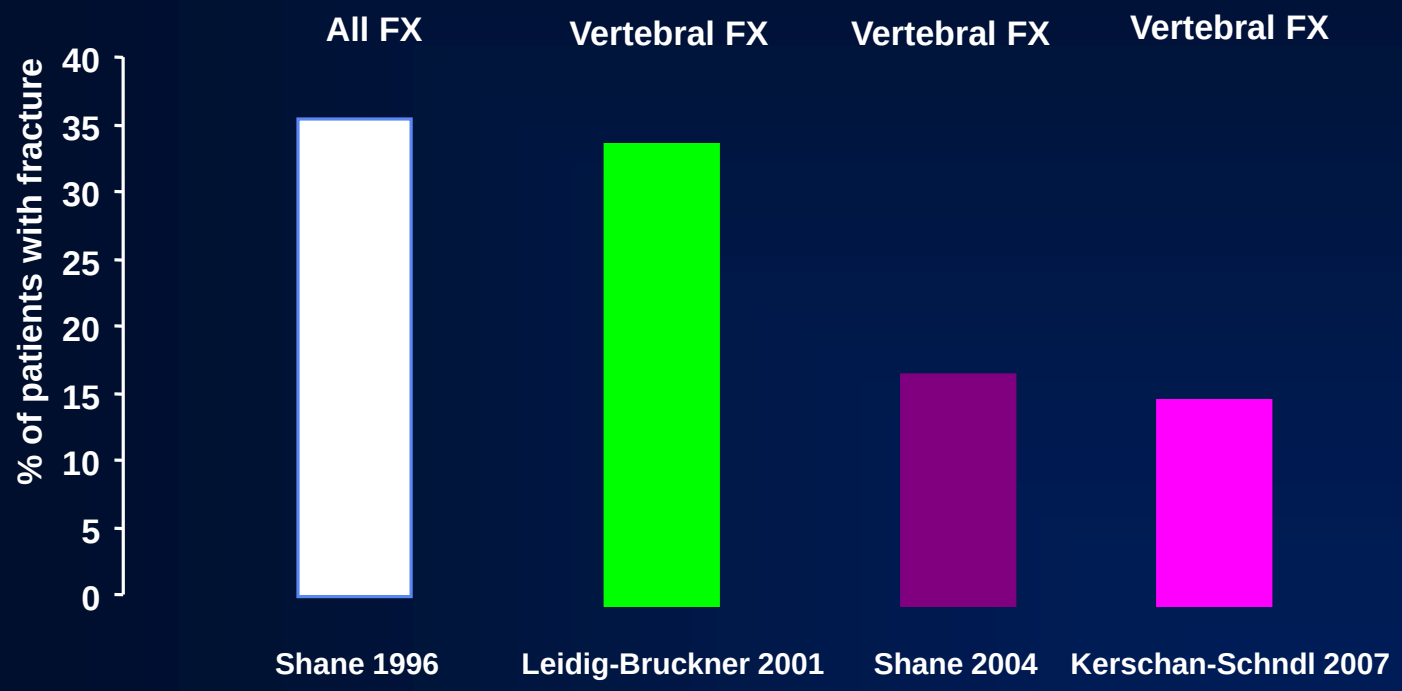


Biochemical Evidence of Uncoupling After Transplantation

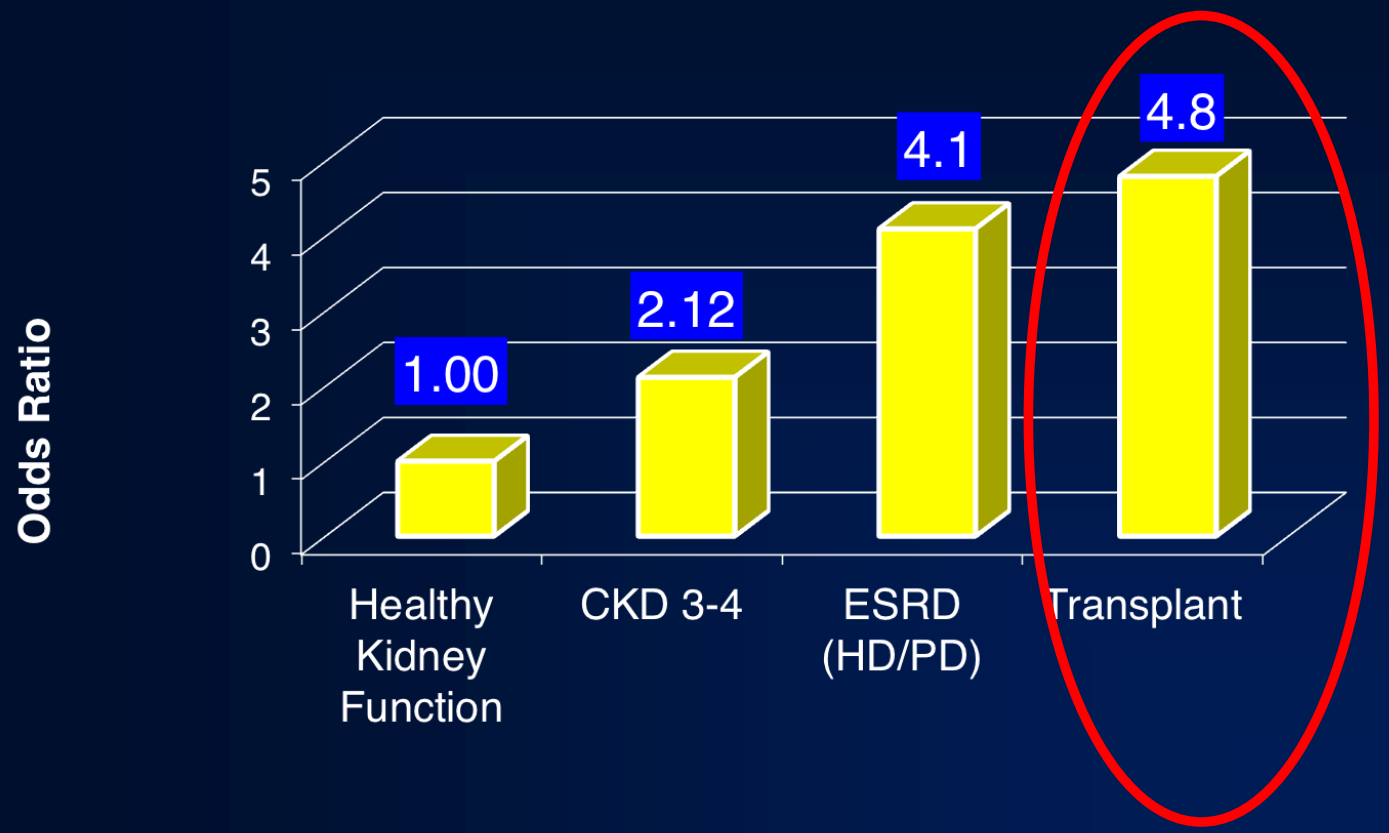


Adapted from Shane, J Clin Endocrinol Metab. 1997;82;1497

Fractures Occur EARLY: During First 1-3 Years After Heart Transplantation



Fracture Risk Higher in Kidney Transplant Than Dialysis Patients



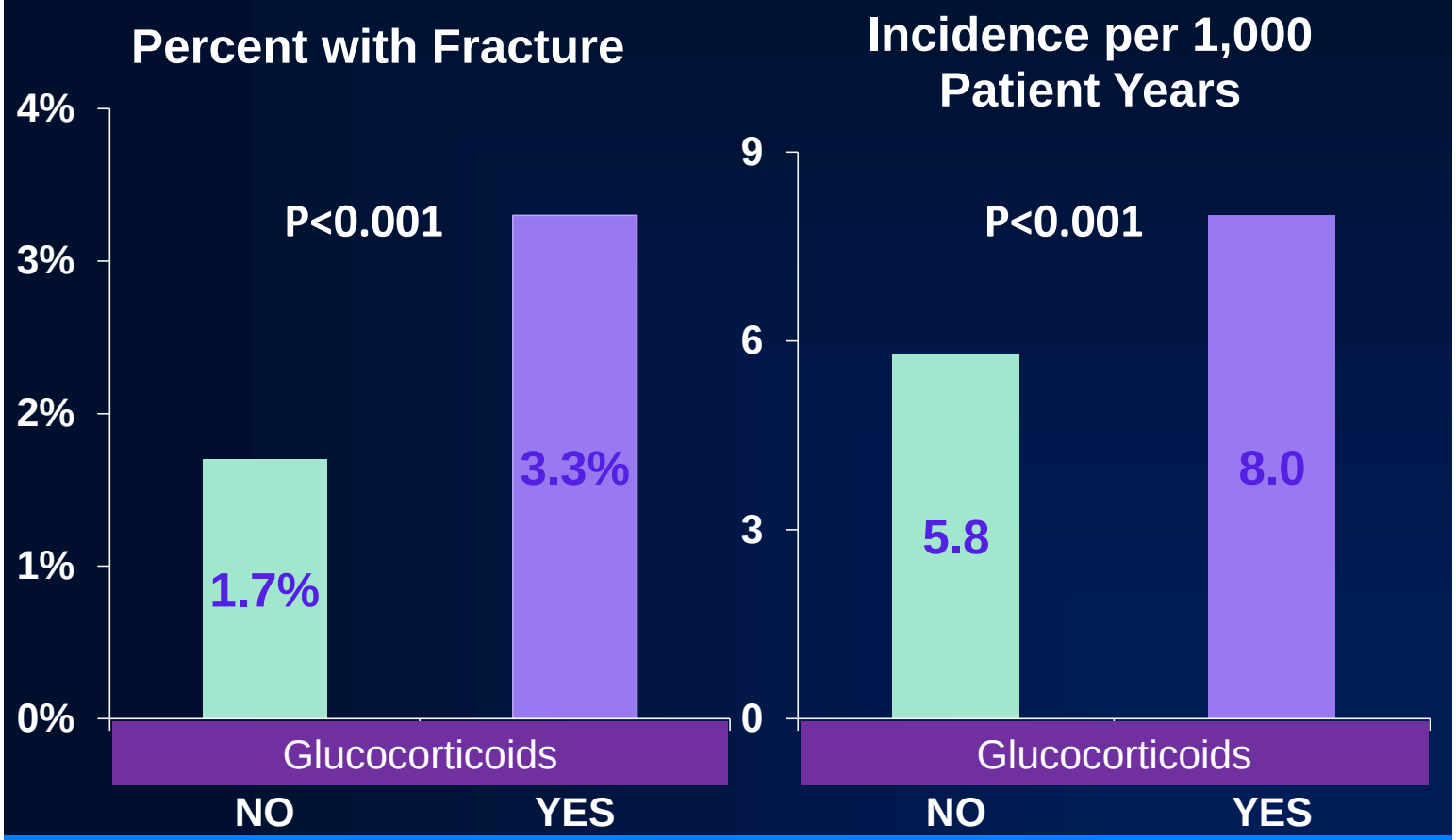
Nickolas et al JASN 2006; Alem et al, KI 2001; Ball et al, JAMA; Vautour et al, OI 2004

Trends in Kidney Transplant Immunosuppression

- Induction therapy
  - Anti-IL2 receptor antibodies, Antilymphocyte and Antithymocyte drugs
- Shift from Cyclosporine to Tacrolimus
- Other changes in maintenance regimens
  - Sirolimus, mycophenolate mofetil

Fewer episodes of rejection
Lower prednisone doses
Less bone loss
Fewer fractures??

Fractures After Kidney Transplant Resulting in Hospitalization: US Renal Data System



Adapted from Nikkel et al., J Am Soc Nephrol, 2012.

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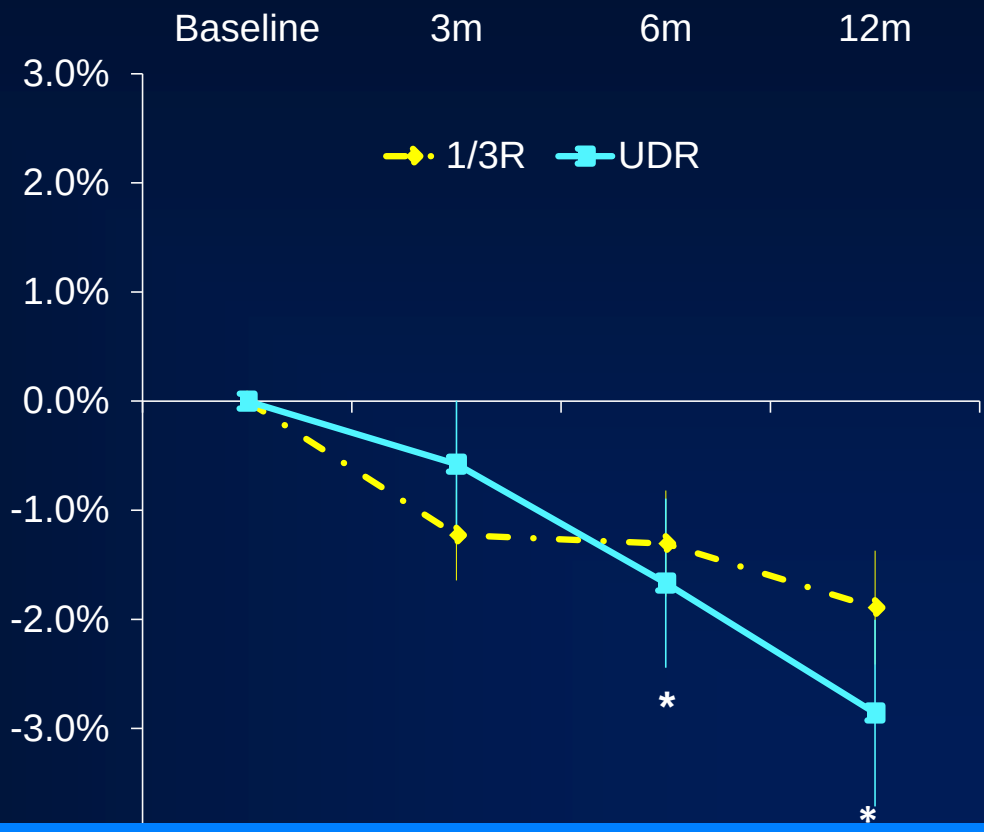
BMD by DXA After Glucocorticoid-Free Kidney Transplant

- Spine
  - No change
- Hip
  - Transient 1-2% decrease
- Forearm
  - Progressive decline



Iyer et al. JASN 2014

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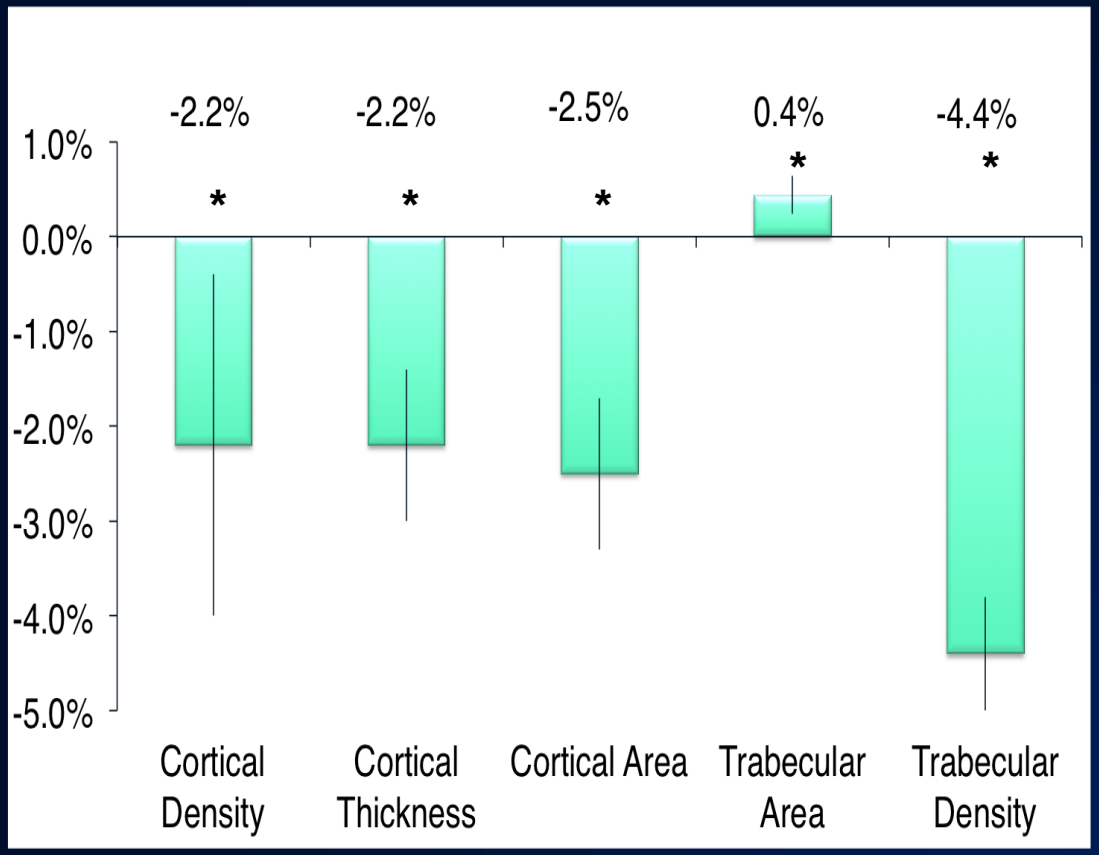
12 Month Changes in vBMD and Microarchitecture After Renal Transplantation



* $p < 0.05$ vs. Baseline

- By HRpQCT, cortical bone loss directly related to higher PTH and BTMs
- Associated with decrease in whole bone stiffness

Adapted from Iyer et al. JASN 2014

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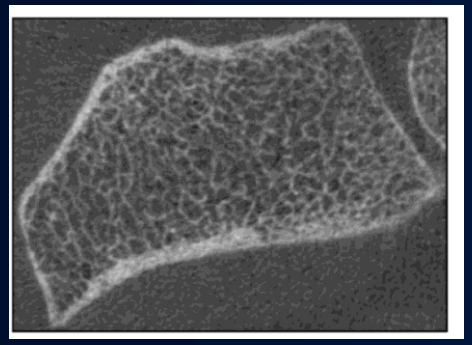
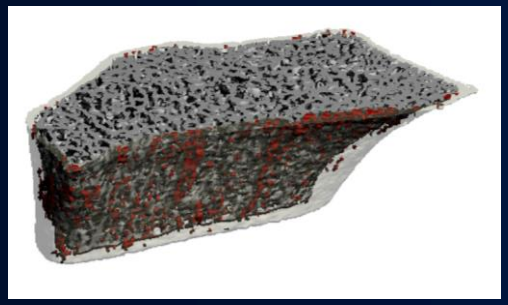
Increased Cortical Porosity One Year After Kidney Transplantation with Glucocorticoid-Free Immune Suppression

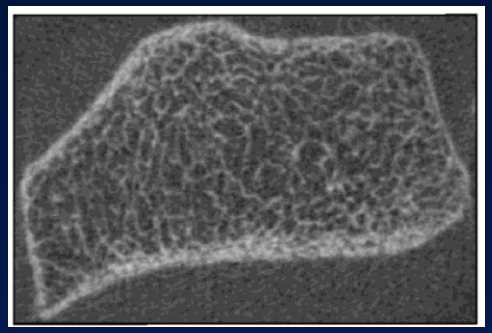
Baseline

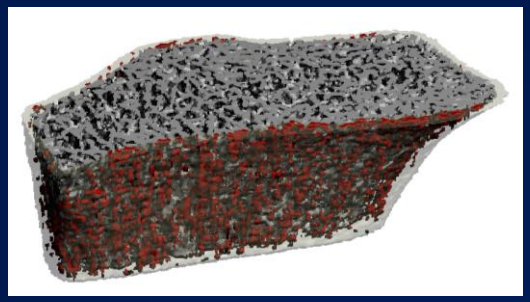




Marked increase in pores (red) after 1 year

1 year





Nishiyama et al. JBMR 2015

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Prevention of Post-Transplant Osteoporosis

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Bisphosphonates and/or Active Vitamin D Metabolites

- Reduce bone resorption by decreasing osteoclast number and activity
- Increase BMD and reduce vertebral fractures in patients on glucocorticoids
- Active vitamin D metabolites also increase intestinal calcium absorption and decrease PTH secretion

Black DM, *Lancet* 1996; Cummings SR, *JAMA*, 1998; McClung M, *New Engl J Med* 2001; Chesnut III CH, *J Bone Miner Res* 2004; Black DM, *N Engl J Med*. 2007; Lyles KW, *N Engl J Med*. 2007; Wallach, *Calcif Tiss Int* 2000; Adachi, Arthr Rheum 2001

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Prevention of Early Post-Transplant Bone Loss

Active Vitamin D metabolites

- Calcitriol or $1,25(OH)_2D$ Sambrook, J Bone Miner Res, 2000
- 1α-OH vitamin D (1α–OHD) De Sevaux, J Am Soc Nephrol, 2002

Oral Bisphosphonates

- Alendronate (Fosamax) Atamaz, OI, 2006; Gil Fraguas, JBMR, 2005; Shane, NEJM, 2004, Shane JCEM 2012
- Risedronate (Actonel, Atelvia) Guadalix, Transpl Int, 2011; Coco, J Am Soc Nephrol, 2012

IV Bisphosphonates

- Pamidronate (Aredia) Monegal, Transpl Int, 2009; Walsh, Am J Kid Dis, 2009
- Zoledronic acid (Reclast) Bodingbauer, AJT, 2007; Crawford, Ann Int Med, 2006; Haas, KI, 2003; Schwartz, KI 2004, Shane JCEM 2012
- Ibandronate (Boniva) Grotz, JASN, 2001; Fahrleitner-Pammer, JBMR, 2009; Kaemmerer, Trans Int, 2010

RANKL Inhibitor

- Denosumab (Prolia) Bonani Am J Transplant, 2016

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Most RCTs Show That Early Intervention Prevents Bone Loss or Increases BMD

- **Kidney**
  - Active vitamin D metabolites, Pamidronate, Zoledronic acid, Ibandronate, Risedronate (women), Denosumab
- **Liver**
  - Alendronate, Pamidronate, Zoledronic acid, Ibandronate
- **Heart**
  - Alendronate, $1,25(OH)_2D$, Ibandronate, Risedronate
- **Lung**
  - Active vitamin D metabolites

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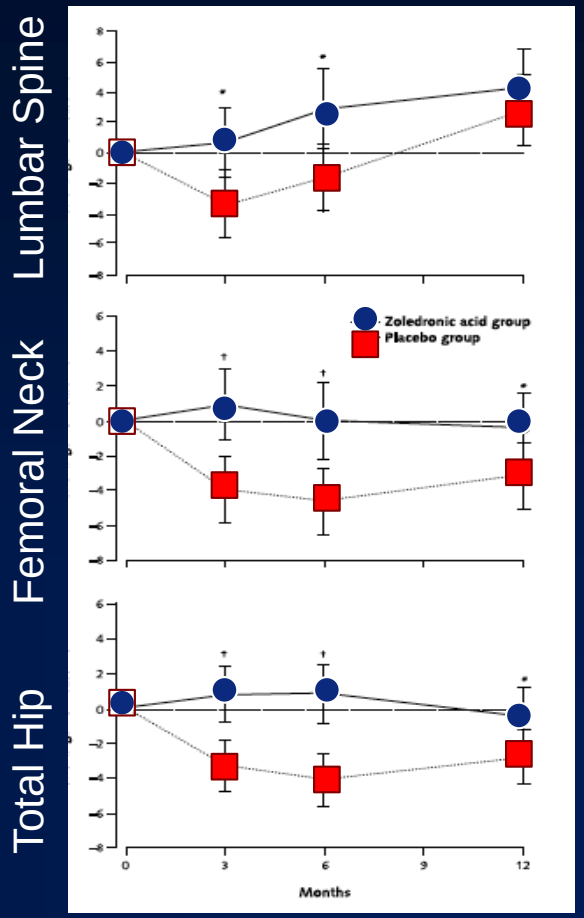
Zoledronic Acid After Liver Transplantation

- N = 62
- Placebo vs. Zoledronic Acid
- Very High Dose
  - 4 mg
  - 1 Week and 1, 3, 6 and 9 Months
- In Zoledronic acid group, no bone loss at
  - Lumbar spine
  - Femoral neck
  - Total hip



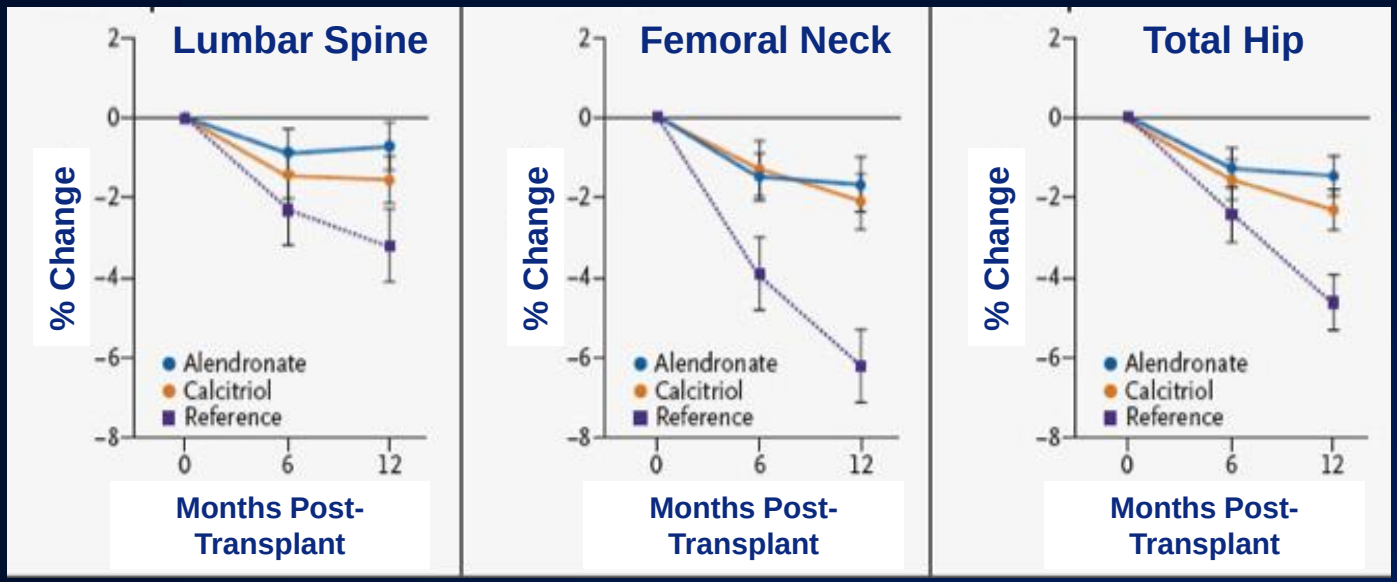
Adapted from Crawford et al, Ann Intern Med 2006

Calcitriol vs. Alendronate After Heart Transplantation

- Randomized, double-blind, double-dummy
- 149 subjects randomized first month after heart Tx
- Alendronate (ALN) - 10 mg QD
  or
- Calcitriol (1,25D) - 0.25 mcg BID
- Treated for first 12 months, then stopped
- Reference group
  - 27 non-randomized, concurrently transplanted, prospectively recruited subjects (REF)

Shane, New Engl J Med. 2004;350:767.

Calcitriol vs. Alendronate: BMD % Change From Baseline



	LS BMD	TH BMD	FN BMD
Alendronate	-0.7%	-1.5%	-1.7%
Calcitriol	-1.6%	-2.3%	-2.1%
Reference	-3.2%*	-4.6%*	-6.2%*

Adapted from Shane, NEJM 2004

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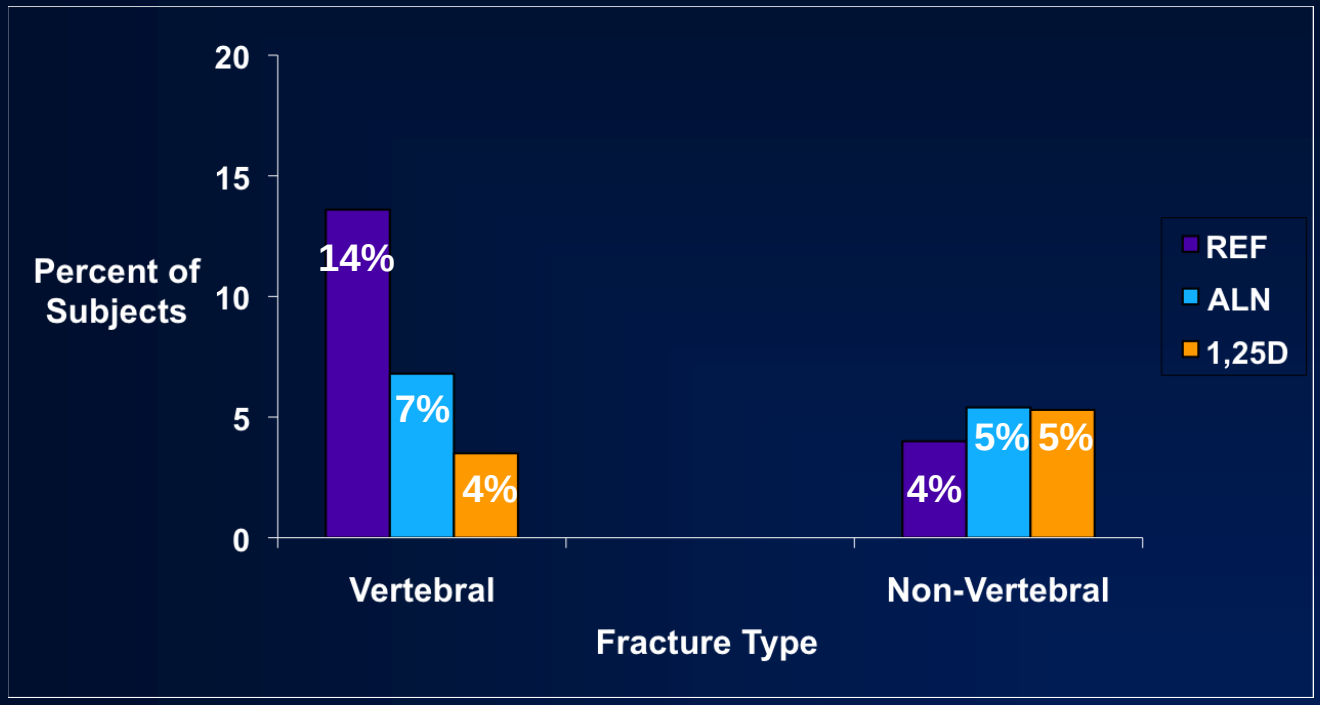
Calcitriol vs. Alendronate After Heart Transplantation: Incident Fractures



Overall fracture rates in controls lower than anticipated
However, there was still a trend toward higher fracture incidence in controls

Shane, New Engl J Med. 2004;350:767.

Calcitriol vs. Alendronate After Heart Transplantation: Year 2 Extension

- 59 subjects who completed RCT on assigned study drug; 16 REF subjects, followed for another 12 months
- T scores > -2.5
- Hypothesis: BMD would decline in the calcitriol group, remain stable in the alendronate group

- BMD stable in all three groups
- No incident fractures

In patients with relatively normal BMD, treatment may be stopped at 1 year without rapid bone loss

Cohen et al., Transplantation, 2006.

Alendronate vs. Zoledronic Acid After Heart or Liver Transplant

84 Heart and Liver Recipients
Randomized during first month after transplant

Zoledronic Acid
5 mg IV Once
or
Placebo

Weekly Alendronate
70 mg PO for 1 year
or
Placebo

Non-randomized
Reference Group
BMD T Score >-1.5

Ergocalciferol 50,000 IU po x 5 days before Zoledronic Acid infusion
Calcium 1000 mg/d and Vitamin D 1000 IU/d

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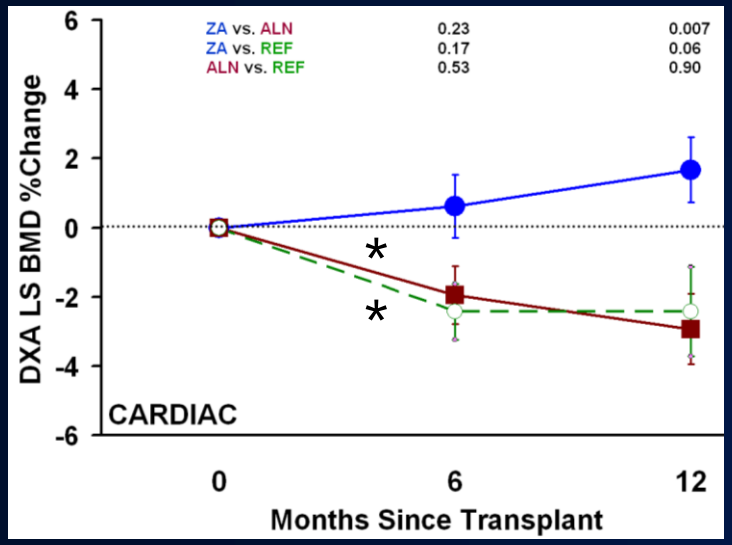
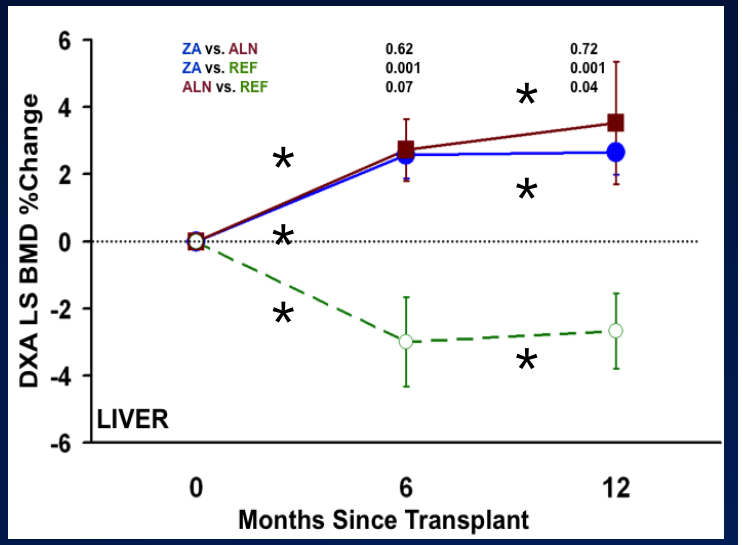
Alendronate vs. Zoledronic Acid
% Change in Lumbar Spine BMD



Heart

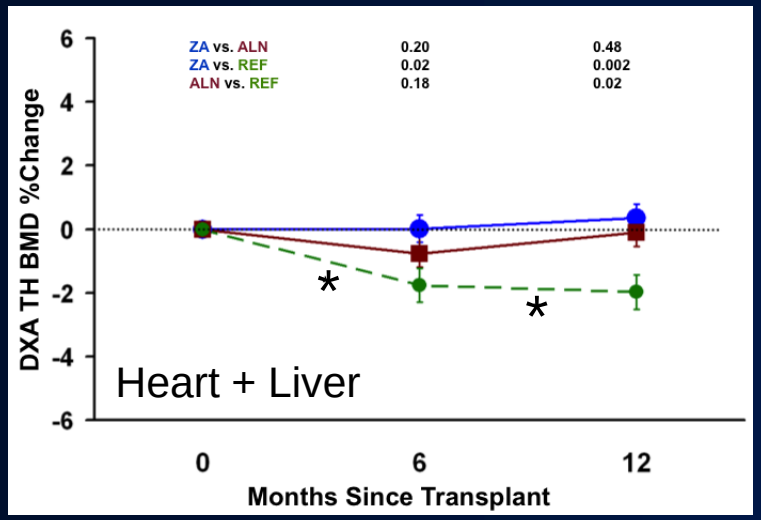


Liver

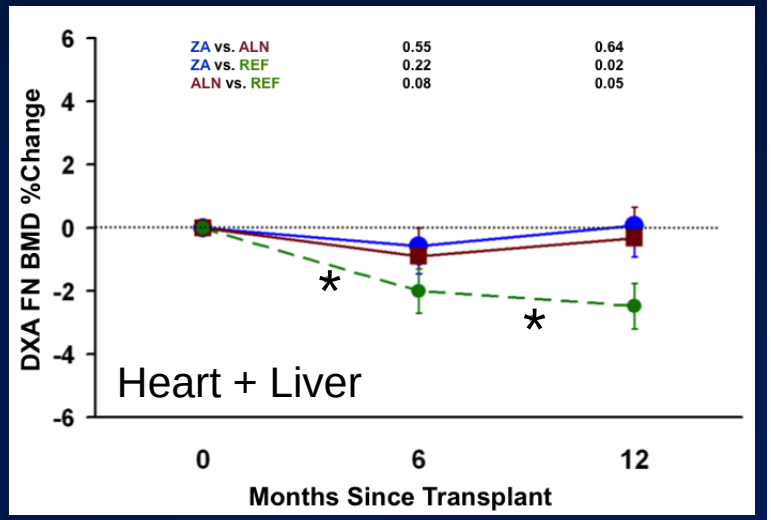
Shane, Cohen, Stein et al., J Clin Endocrinol Metab 2012.

Alendronate vs. Zoledronic Acid: % Change Total Hip & Femoral Neck BMD

Total Hip



Femoral Neck



No Difference in Effect by Heart vs. Liver Transplant

Shane, Cohen, Stein et al., J Clin Endocrinol Metab 2012.

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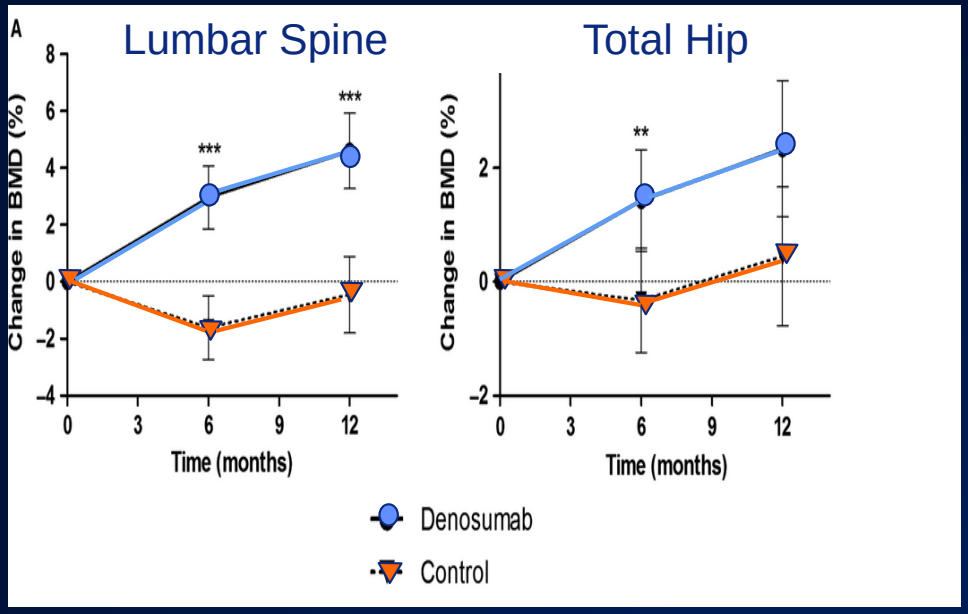
Alendronate vs. Zoledronic Acid Conclusions

- Significant bone loss (~3%) in untreated patients after heart or liver transplant
- No hip bone loss with either zoledronic acid or alendronate
- In liver transplant recipients, both zoledronic acid and alendronate prevent bone loss at the spine
- In heart transplant recipients, zoledronic acid provided greater protection at the spine than alendronate

Shane, Cohen, Stein et al., J Clin Endocrinol Metab 2012.

Effect of Denosumab on Prevention of Bone Loss After Kidney Transplant

- 90 patients
- Randomized within 2 weeks of transplant to Denosumab or placebo
- Received 2 doses



Dmab: Significant improvement in BMD at LS and TH

Adapted from Bonani et al. Am J Transplant 2016.

Denosumab After Transplant: Safety Considerations

- Infection:
  - In RCT of renal transplant recipients, increased UTIs, incidence of other infections similar to control group
- Hypocalcemia:
  - Increased in RCT of renal transplant recipients
  - After heart and lung transplant, reports of severe hypocalcemia
  - Greater risk in patients with low baseline eGFR, despite normal calcium and 25OHD
- Rebound bone loss and vertebral fractures:
  - Complicate discontinuation of treatment

Bonani et al. Transplantation 2017; Shrosbree et al. Intern Med J 2018

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Prevention of Post-Transplant Fractures

Intervention Studies and Fracture Incidence

- Most intervention studies show preservation of BMD
- Majority not powered to detect differences in fracture
- Reduction in fractures reported in 4 RCTs
  - Others found no significant difference or did not report fractures because of small numbers
- Lack of evidence that intervention prevents fractures has led to reluctance to implement prevention protocols after transplantation

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Meta-analysis: Prevention of Fracture After Solid Organ Transplant

Aim: To determine whether treatment reduces risk of fracture in the first year post-transplant

INCLUSION CRITERIA

- Randomized clinical trials
- Solid organ transplant
  - Liver, kidney, heart, lung
- Patients followed from transplant
- Treatment and control group (±placebo)
- Fracture assessment by x-ray
- Bisphosphonates (oral/ IV)

  Or

  Active vitamin D analogues

EXCLUSION CRITERIA

- Historical controls
- Other treatments
  - HRT
  - Calcitonin (as active treatment)
  - Resistance exercise
- Pediatric populations
- Studies comparing two treatments

Stein et al, J Clin Endocrinol Metab, 2011

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Included Studies

Trial	Organ	Subject	Rx	Subjects With Fractures		Total Fractures	
				Rx	Con	Rx	Con
Bodingbauer, 2007	Liver	69	ZA	4	11	4 (4)	11 (11)
Crawford, 2006	Liver	54	ZA	2	2	2 (0)	10 (9)
Fahrleitner-Pammer, 2009	Heart	35	IBD	2	9	2 (2)	17 (17)
Gil Fraguas, 2005	Heart	87	ALN	3	7	7 (6)	15 (15)
Grotz, 2001	Kidney	72	IBD	2	2	2 (1)	2(1)
Kaemmerer, 2010	Liver	74	IBD	2	7	2 (1)	8 (4)
Monegal, 2008	Liver	79	PAM	7	3	15 (13)	3 (2)
Schwarz, 2004	Kidney	20	ZA	1*	1*	1(1)*	1(1)*
Walsh, 2009	Kidney	125	PAM	2	5	2 (0)	5(1)
De Seveaux, 2002	Kidney	109	1α-OHD	0.5*	4.5*	0.5 (0.5)*	12.5 (6.5)*
Sambrook, 2000	Heart/Lung	65	1,25$(OH)_2$D	1*	2*	1(1)*	11 (11)*

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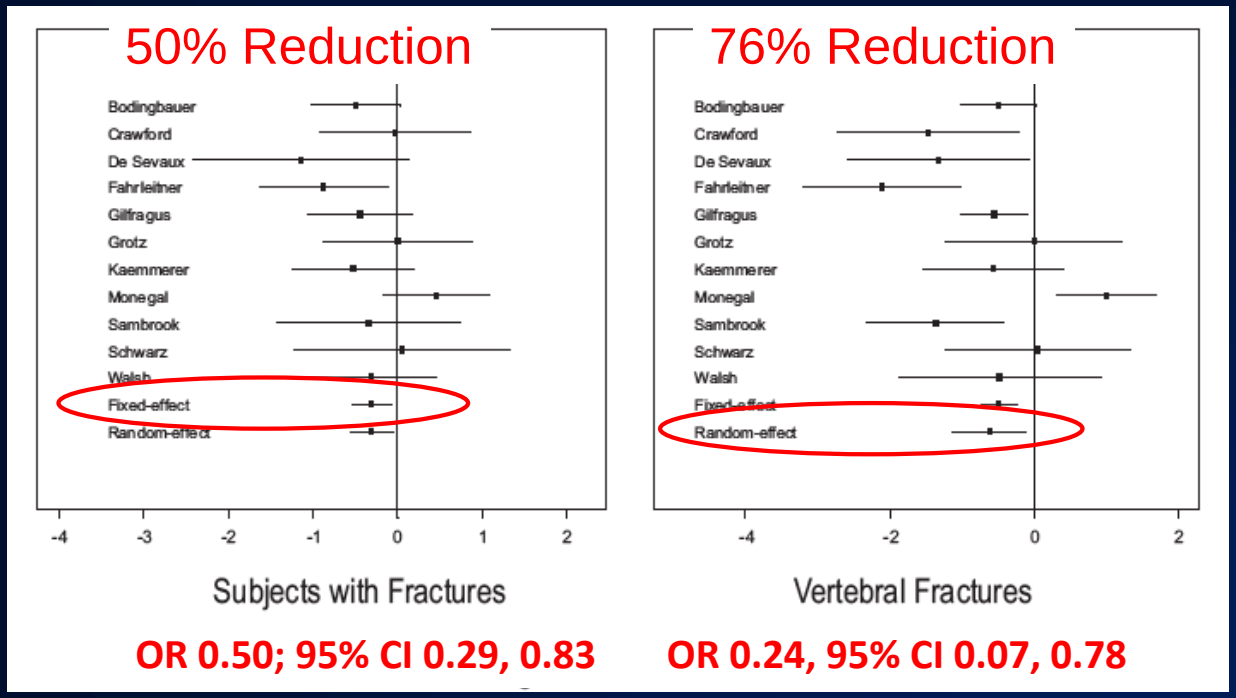
Bisphosphonates or Active Vitamin D Analogues: Effect on Fractures

11 studies: 780 patients, 134 fractures

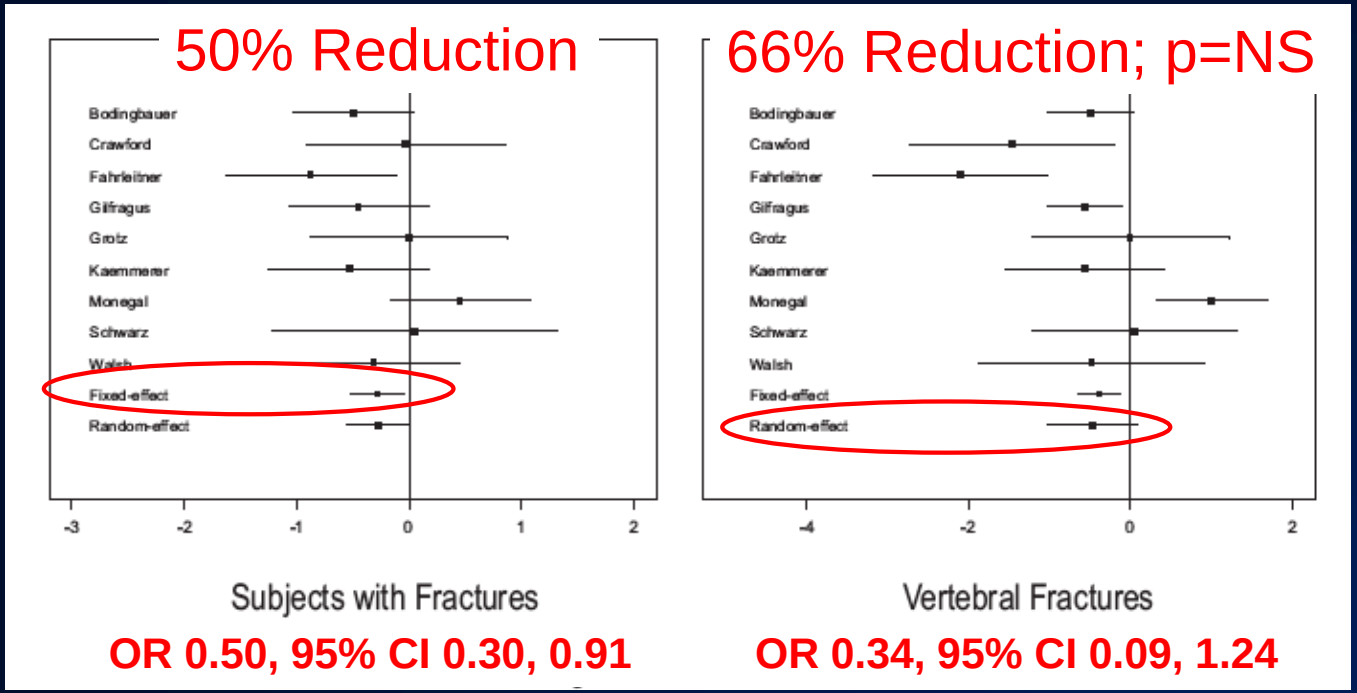
Fracture Incidence in untreated patients 24.7%



Stein et al, J Clin Endocrinol Metab, 2011

Bisphosphonate Studies Only: Effect on Fractures

9 studies: 737 subjects, 116 fractures



Stein et al, J Clin Endocrinol Metab, 2011

Meta-Analysis Summary

- Limitations:
  - Heterogeneity of studies
  - Variable quality of reported data
  - Limited access to raw data
  - May not be generalizable to patients on newer immunosuppressive regimens
    - Lower glucocorticoid doses, FK 506 instead of Cyclosporine A
- Treatment with bisphosphonates or active vitamin D analogues during the first year after solid organ transplant is associated with reduced risk of fracture

Stein et al, J Clin Endocrinol Metab, 2011

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Management of Bone Disease Post-Transplant

Approach to Fracture Prevention After Heart, Liver, or Lung Transplantation

Before or at time of transplant

- BMD by DXA and spine radiographs
- Measure serum 25OHD

Fracture Risk Assessment

- Age > 50, postmenopausal woman, prior fracture, diabetes, BMD T scores

All patients

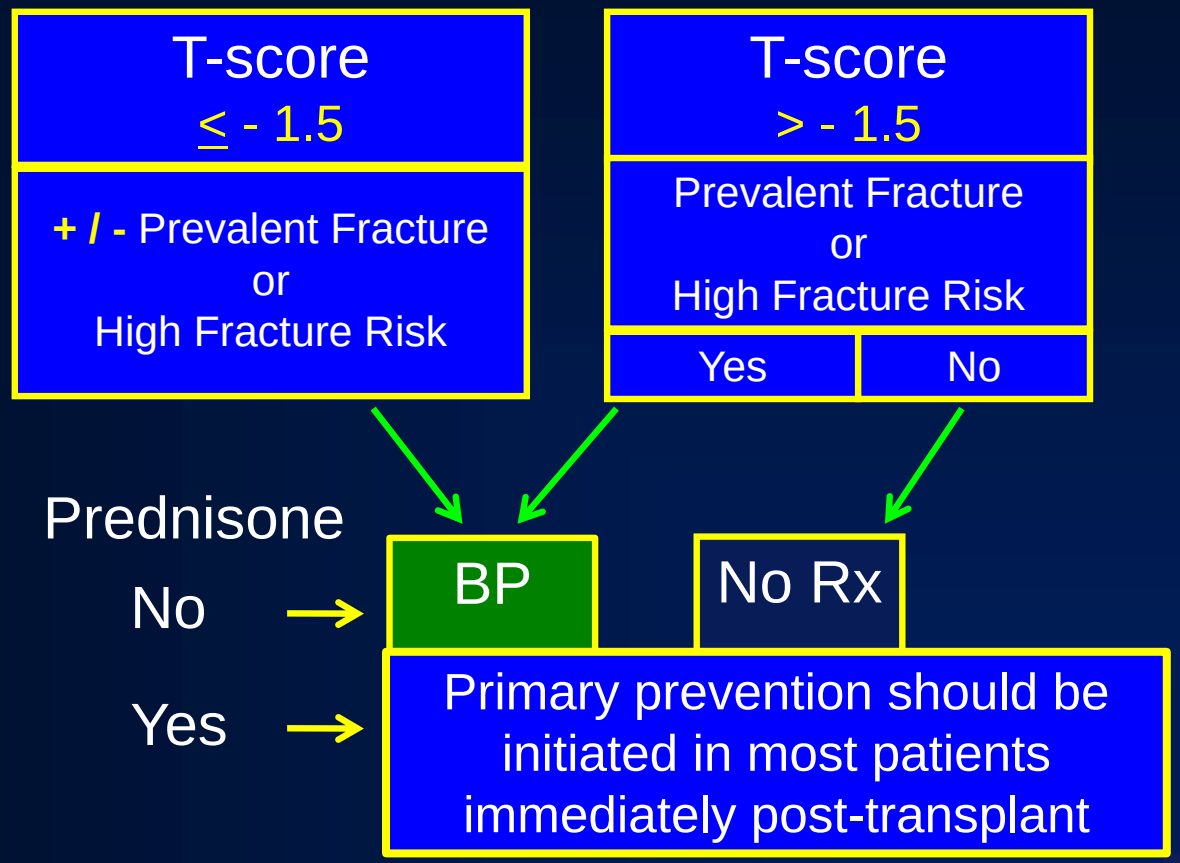
- Replete vitamin D to 30 ng/ml
- Calcium (Diet + supplements = 1000-1200 mg/d)
- Weight bearing exercise

American College of Rheumatology 2017 Guidelines for Management of GIOP

- Treat adult solid organ transplant recipients with eGFR>30 ml/min who continue glucocorticoids according to general GIOP guidelines
- Treat patients at moderate or high risk for fracture
  - Prior fracture, DXA T-Score/Z-Score, FRAX, GC dose
- Refer all renal transplant to Metabolic Bone expert
- Recommend against denosumab because of lack of safety data

Buckley Arthritis & Rheumatology 2017

Treatment Allocation: PM Women and Men
BMD, Fracture, Risk Factors, Steroids



Management of Bone Disease After Kidney Transplant

Management Considerations After Kidney Transplant (KTx)

- Use of bisphosphonates controversial after KTx
  - Prolonged residence in bone
  - Long duration of action
  - Potential to cause adynamic bone disease or increase PTH
- Bisphosphonates and vitamin D analogues increase/preserve bone mass after KTx
- Lack of evidence that therapy with bisphosphonates or vitamin D analogues prevents fractures
- Denosumab may be an option for patients in whom other agents are contraindicated or have been unsuccessful
- Teriparatide not routinely recommended, possible role in patients with low-turnover bone disease and osteoporosis

Wilson et al. Ann Intern Med 2017; Mitterbauer et al. Nephrol Dial Transplant 2006; Versele et al. Transpl Int 2016; Toth-Manikowski et al. Clin Transplant 2016; Cejka et al. Am J Transplant 2008

KDIGO Guidelines for Transplant Bone Disease

Prior to transplant, treat hyperparathyroidism

- Surgical treatment only for patients who fail medical management

After transplant, if eGFR > 30ml/min/1.73 m^2 :

- Measure BMD during first 3 months after KTx if receiving glucocorticoids or other risk factors for osteoporosis
- If BMD low and patient within 12 months of transplant:
  - Consider treatment with vitamin D, calcitriol/alfacalcidiol, or bisphosphonates
- Consider bone biopsy to guide treatment *before* using bisphosphonates because of high incidence of adyanamic bone disease
  - Bone biopsy not widely available
  - Could result in considerable delays in initiating treatment

KDIGO Clinical Practice Guideline for CKD-MBD, Kidney Int Suppl 2017; 2020 Clinical Practice Guideline on Evaluation and Management of Candidates for Kidney Transplantation

Risk-Based Approach to Management After Kidney Transplantation

Before or at time of transplant

- PTH, 25-OHD, BMD by DXA and spine radiographs

2-4 weeks after transplant

- PTH, 25-OHD
- Bone turnover markers (BSAP, P1NP or CTx)

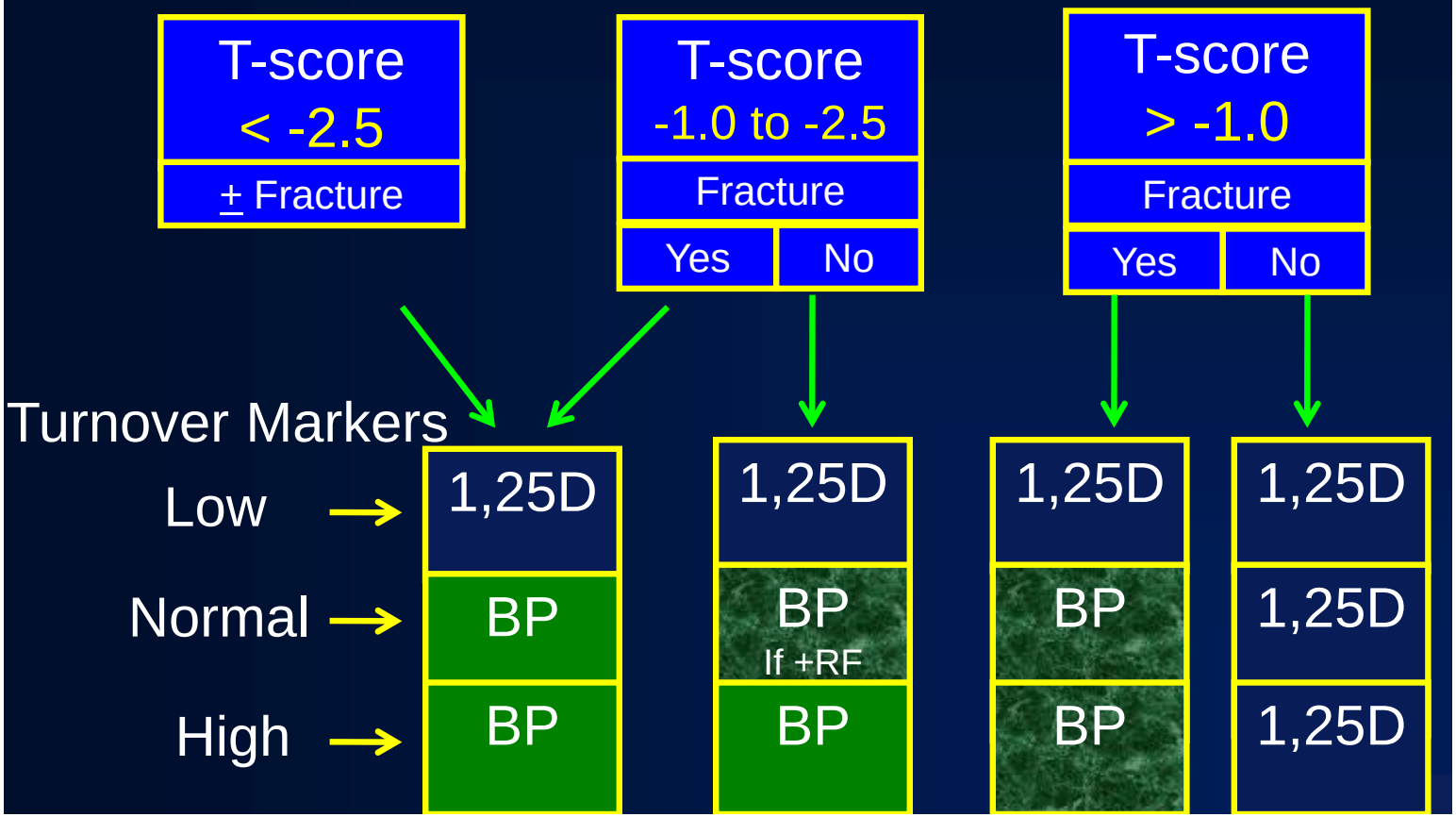
All patients

- Regular weight bearing exercise
- Replete vitamin D with cholecalciferol
- Calcium (Total intake - 1000 mg/d), if no hypercalcemia
- Treat persistent hyperparathyroidism

Mainra and Elder, Clin J Am Soc Nephrol 2010

Treatment Allocation: Kidney Transplant
BMD, Fracture, Turnover

Adapted from Mainra and Elder, Clin J Am Soc Nephrol 2010



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Summary

- Osteoporosis and fractures are common before transplantation
  - Disease related factors
  - Chronic illness
  - Vitamin D Deficiency
  - CKD
  - Medications
- Osteoporosis after transplantation is multi-factorial
- Bone loss occurs early after transplant, first 6 months
- Glucocorticoid-sparing regimens may prevent some (but not all) fractures

Summary

- All patients should be evaluated before and receive treatment for prevalent osteoporosis
- Primary prevention therapy should be initiated immediately after transplant in patients with risk factors
- Long-term transplant recipients should be monitored and treated for bone disease
- Bone loss (and probably fractures) can be prevented by early intervention with bisphosphonates or vitamin D analogues
- Additional data is needed on the safety and efficacy of anabolic medications and denosumab

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Conclusions

- There has been tremendous progress in the past 30 years elucidating the natural history, pathogenesis and potential treatment strategies for transplantation osteoporosis.
- Transplantation osteoporosis remains a significant problem, with unacceptably high rates of bone loss and fractures.
- With proper vigilance, early diagnosis, and treatment, transplant osteoporosis is preventable.

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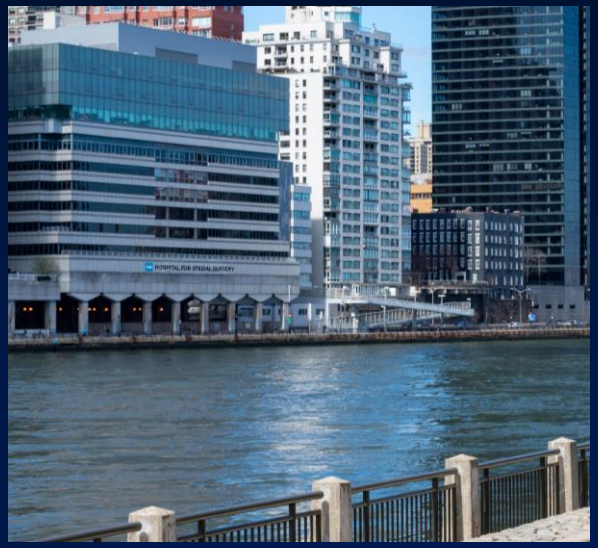

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