



Post transplantation osteoporosis

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Outlines

- Introduction to osteoporosis
- Pathophysiology of post transplantation osteoporosis
- Diagnosis
- Treatment options

Introduction: The elements of bone strength



Introduction







Question

- What kinds of KT drugs is safe for osteoporosis development?
- 1. Azathioprine
- 2. Tacrolimus
- 3. Cyclosporine
- 4. Mycophenolate
- 5. None

Epidemiology



Nikkel LE, Hollenbeak CS, Fox EJ, Uemura T, Ghahramani N: Risk of fractures after renal transplantation in the United States. Transplantation 87: 1846–1851, 2009

Weisinger JR, Carlini RG, Rojas E, Bellorin-Font E: Bone disease after renal transplantation. Clin J Am Soc Nephrol 1: 1300–1313, 2006

Malluche HH, Monier-Faugere M-C, Herberth J: Bone disease after renal transplantation. Nat Rev Nephrol 6: 32–40, 2010

Frequency of monitoring: CKD G3a–G5D

G1T	G2T G3aT G3bT	G4T	G5T
	↓Vitamin D, ↓Ca, 🕇	PO, 🕇 PTH, 🕇 FGF-23	t Ca
Ca, PO, PTH and alkaline phosphatase activity	 G1T-G3bT: Serum Ca and PO, every 6-12 months PTH, once, subsequent intervals based on CKD progression Alkaline phosphatase, every 12 months (from G3aT)* 	 G4T: Serum Ca and PO, every 3–6 months PTH, every 6–12 months Alkaline phosphatase, every 12 months* 	 G5T: Serum Ca and PO, every 1–3 months PTH, every 3–6 months Alkaline phosphatase, every 12 months*
a	G1T-G5T:		

25(OH)D levels might be measured, and repeated testing determined by baseline values and therapeutic interventions

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Question:

- Do you do BMD by DEXA for your KT patients, routinely?
- Yes
- No

Question

- When do you evaluate KT patients after surgery?
- 1. First 3 months
- 2. First 6 months
- 3. First 6-12 months
- 4. After 1 year

Osteoporosis

• A reduction in bone mass + micro-architectural deterioration of bone tissue increase in bone fragility and susceptibility to fracture.



Osteopenia



Risk factors for osteoporosis

General factors

Younger age at transplantation

Poor nutrition

Smoking

Alcohol abuse

Endocrine/mineral factors

Hypogonadal status

Hypomagnesemia: CNI, PPI

Biologic abnormalities

Functionally different alleles of the vitamin D receptor gene

post transplantation osteoporosis

Evaluation of patients with post-transplant osteoporosis

- History/Physical
- H/O recent fracture
- Back pain/bone pain
- Family H/O osteoporosis
- Exercise
- Smoking cessation
- Alcohol cessation

• Serologies

- Serum calcium level
 - Serum phosphorous level
 - Serum parathyroid level
 - Estrogen levels
 - Progesterone level
 - TSH level

• FRAX

- Predicts 10% fracture risk
- DEXA-scan Annually

FRAX

Calculation Tool

• 1

Please answer the questions below to calculate the ten year probability of fracture with BMD.





DEXA





When I should treat patients?

- In those with hip or vertebral (clinical or asymptomatic) fractures
- In those with T-scores ≤–2.5 at the femoral neck, total hip, or lumbar spine by DXA
- In postmenopausal women and men age 50 and older with low bone mass (T-score between -1.0 and -2.5, osteopenia) at the femoral neck, total hip, or lumbar spine by DXA and a 10-year hip fracture probability ≥3 % or a 10-year major osteoporosis-related fracture probability ≥20%.

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/ AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS— 2020 UPDATE *V/*Y/Y*** post transplantation osteoporosis

Pharmacologic options

- Bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid)
- Calcitonin
- Estrogen agonist/antagonist (raloxifene)
- Estrogens and/or hormone therapy
- Tissue-selective estrogen complex (conjugated estrogens/bazedoxifene)
- Parathyroid hormone 1–34 (teriparatide)
- Receptor activator of nuclear factor kappa-B (RANK) ligand inhibitor (denosumab)

Effect on BMD

Intervention	Vertebral fracture	Non-vertebral fracture	Hip fracture
Alendronate	A	A	A
Ibandronate	A	A*	NAE
Risedronate	A	A	A
Zoledronic acid	A	A	A
Calcitriol	A	NAE	NAE
Denosumab	A	Α	A
HRT	A	A	A
Raloxifene	A	NAE	NAE
Teriparatide	A	A	NAE

Anti-resorptive Agents

- Inhibit osteoclast mediated bone resorption:
- THEREFORE: use in treatment of patients with high turnover bone disease;
- Contraindicated in patients with low turnover or adynamic bone disease

Bisphosphonates

• Inhibit farnesyl pyrophosphate synthase



Why do bisphosphonates continue to inhibit bone resorption for many years after stopping?

- Mechanism 1
 - Bisphosphonates bind to bone
 - Alendronate more than risedronate
 - They are taken up by the osteoclast and inhibit bone resorption
 - The half life of alendronate is estimated at 10 years





Baron R, et al. Bone. 2011 Apr 1;48(4):677-92

Bisphosphonates

- These agents have not been recommended in patients with eGFR < 30 mL/min.
- Alendronate:
- For the prevention (5 mg daily and 35 mg weekly tablets) and treatment (10 mg daily tablet, 70 mg weekly tablet)
- Reduces the incidence of spine and hip fractures by about 50 % over 3 years in patients with a prior vertebral fracture or in patients who have osteoporosis at the hip site.

Bisphosphonates

• **Zoledronic acid**: 5 mg by intravenous infusion over at least 15 min once yearly for treatment and once every 2 years for prevention)



• **Risedronate**: prevention and treatment (5mg daily tablet; 35 mg weekly tablet)



Clinician's Guide to Prevention and Treatment of Osteoporosis. DOI 10.1007/s00198-014-2794-2 post transplantation osteoporosis

Nested case control study

Background



Bisphosphonates have been commonly prescribed to improve mineral and bone disorders in kidney transplant recipients (KTR)



Results

kidney transplantation outcomes

Effects of bisphosphonates on long-term

Safety of bisphosphonate use on renal allograft function is unclear beyond 2 years of treatment

Methods

3836 KTR (April 1979–June 2016)

Incidence density sampling (1:1) of KTR:

Graft failure (n=1160)
No graft failure (n=1160)

Annual bone density assessments

Bisphosphonates prescribed for osteopenia or osteoporosis

Outcomes: • Long-term graft outcome



Graft failure (Adjusted* OR) 0.40 (95% Cl 0.31-0.51) p<0.001



*Adjusted for recipient age, sex, hypertension, diabetes; donor age, sex, relation; HLA mismatch, ABO incompatibility, re-transplantation, immunosuppressant, vitamin D use, acute rejection and baseline eGFR

Conclusion

Bisphosphonates may improve long-term graft survival in kidney transplant recipients



Song, S.H., et al. NDT (2020)

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Calcitonin



- Use in women who are at least 5 years postmenopausal when alternative treatments are not suitable.
- Has not been shown to increase BMD in early postmenopausal women.
- In KT: Studies are scarce

Current Status of Research on Osteoporosis after Solid Organ Transplantation: Pathogenesis and Management. BioMed Research International Volume 2015, Article ID 413169. http://dx.doi.org/10.1155/2015/413169. v/. Y/199. post transplantation osteoporosis

Clinician's Guide to Prevention and Treatment of Osteoporosis. DOI 10.1007/s00198-014-2794-2

Teriparatide



- In postmenopausal women and men at high risk for fracture
- In sustained systemic glucocorticoid therapy.
- 20 µg daily subcutaneous injection
- If and when treatment is stopped, bone loss can be rapid and alternative agents should be considered to maintain BMD.
- In KT: Only limited data are available on teriparatide therapy for patients receiving organ transplantation

Current Status of Research on Osteoporosis after Solid Organ Transplantation: Pathogenesis and Management. BioMed Research International Volume 2015, Article ID 413169. http://dx.doi.org/10.1155/2015/413169. v/. Y/199. post transplantation osteoporosis

Clinician's Guide to Prevention and Treatment of Osteoporosis. DOI 10.1007/s00198-014-2794-2

RANKL/RANKL inhibitor: Denosumab



- 60 mg every 6 months as a subcutaneous injection.
- Hypocalcemia must be corrected before starting
- If and when denosumab treatment is stopped, bone loss can be rapid and alternative agents should be considered to maintain BMD.
- In KT: improves bone density and bone quality in first-year kidney transplant recipients at risk to develop osteoporosis.

Clinician's Guide to Prevention and Treatment of Osteoporosis. DOI 10.1007/s00198-014-2794-2

Hormone Replacement Therapy (HRT)

- Reduce the risk of osteoporosis in menopausal women.
- In KT: restricted literature

Current Status of Research on Osteoporosis after Solid Organ Transplantation: Pathogenesis and Management. BioMed Research International Volume 2015, Article ID 413169. http://dx.doi.org/10.1155/2015/413169.v/.t/\ft. Clinician's Guide to Prevention and Treatment of Osteoporosis. DOI 10.1007/s00198-014-2794-2

Remember

• There are insufficient data to guide treatment after the first 12 months.

• It seems : like non KTp should be done

Question

- After starting Bisphosphonate, when do you repeat DEXA?
- 1. In Alendronate use, after 24months
- 2. In Zoledronate use, after 36months
- 3. In Bisphosphonate use, as a whole, after 5 years
- 4. In Bisphosphonate use, as a whole, every 1 year

Algorithm for long-term treatment monitoring





Calcium preparations

Calcium carbonate	40% elemental calcium
Calcium citrate	21% elemental calcium
Calcium gluconate	9% elemental calcium
Calcium lactate	13% elemental calcium

Calcium citrate is absorbed equally well when taken with or without food and is a form recommended for individuals with low stomach acid (more common in people over 50 or taking acid blockers), inflammatory bowel disease or absorption disorders

Calcium Citrate

Dietary Suppleme Calciur fort

Minoo®

With 1000 mg Calcium &

2000 IU Vitamin D per di for the maintenance of norma Bones

Manganese, Cop Vitamin 86 and 1

In brief

- Post transplantation osteoporosis must be considered for Tx in first year.
- BMD and FRAX is necessary for evaluation.
- Bisphosphonate (PO or parenteral) is preferred
- Denosumab is another choice(use in eGFR<30cc/min/1.73m2)
- Repeat DEXA after 3-5 years after starting with unclear guidance

Thank you for your attention! post transplantation osteoporosis 34