MBD(Mineral Bone Disorder) after renal transplantation

Sepideh hajian
Assistant professor
Ghazvin university of medical sciences

outline

- Epidemiology
- Pathophysiology
- Clinical presentation
- Evaluation
- treatment

Introduction

- **Bone and mineral disorders occur frequently in kidney transplant recipients and are associated with a high risk of fracture, morbidity, and mortality.**
- **is a broad spectrum of often overlapping bone diseases seen after transplantation, including osteoporosis as well as persisting high– or low–turnover bone disease*.**
- **It is associated with disturbances in the homeostasis of phosphate, calcium, calcitriol, fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH).**

- *Sukumaran Nair S, Lenihan CR, Montez-Rath ME, Lowenberg DW, Chertow GM, Winkelmayer WC: Temporal trends in the incidence, treatment and outcomes of hip fracture after first kidney transplantation in the United States. Am J Transplant 14: 943–951, 2014

Epidemiology

- Earlier studies after transplantation indicate that bone mineral density (BMD) declines by 4%–10% in the first 6 months, with a further decrease of 0.4%–4.5% in lumbar BMD between 6 and 12 months* .

- After 1 year, BMD remains relatively stable with no further decline but at significantly **lower levels than healthy controls**.

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

- This reduction in BMD contributes to an increased risk of fractures.
- In the first 5 years after transplantation, 22.5% of kidney transplant recipients experience a fracture—an incidence that is **four times** that in the general population *.
- This risk remains significantly elevated even 10 years post-transplantation, suggesting that bone remains fragile after transplantation, despite improvement in parameters of mineral metabolism.
- The **fracture rate** among kidney transplant recipients is 34% higher **in the first 3 years after** transplantation, but thereafter, the risk of fracture is lower than that in comparable patients who remain **on dialysis** . The most common fracture locations are the hip and ankle/foot**.

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

Ball AM, Gillen DL, Sherrard D,Weiss NS,Emerson SS, Seliger SL, etal :Risk of hip fracture among dialysis and renal transplant recipients. JAMA **288: 3014–3018, 2002

LE,

- The rate of fracture has decreased in recent years, with the USRDS data showing the incidence of **hip fracture** to be **45% lower** in patients transplanted in 2010 than in patients transplanted in 1997*due to:
- 1-significant reduction in cumulative glucocorticoid (GC) exposure
- 2-improved management of CKD-MBD pretransplantation and bone protection strategies, such as vitamin D and bisphosphonates in kidney transplant recipients
- 3-changes in lifestyle and physical activity

outcomes after **hip fracture** are poor, with a recent analysis of 21,769 kidney transplant recipients in the United Kingdom indicating that a hip fracture was independently associated with a threefold increase in mortality risk**.

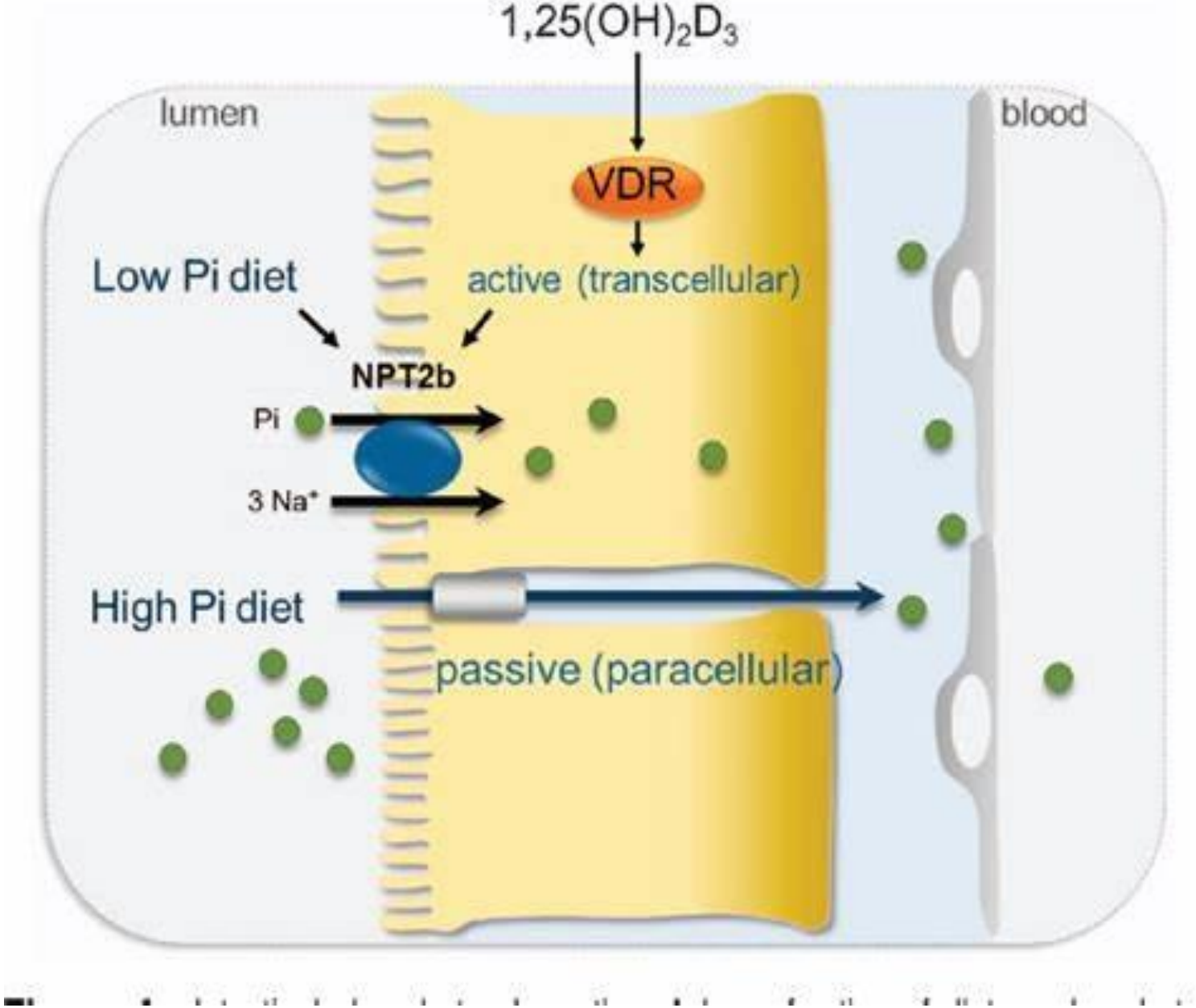
*Nikkel LE, Mohan S, Zhang A, McMahon DJ, Boutroy S, Dube G, Tanriover B, Cohen D, Ratner L, Hollenbeak CS, Leonard MB, Shane E, Nickolas TL: Reduced fracture risk with early corticosteroid withdrawal after kidney transplant. Am J Transplant 12: 649–659, 2012

Arnold J, Bagnall D, Ray D, Sharif A: Fracture risk and mortality post-kidney transplantation. Clin Transplant **29: 1004–1012, 2015

Pathophysiology of Post–Transplant Bone Disease

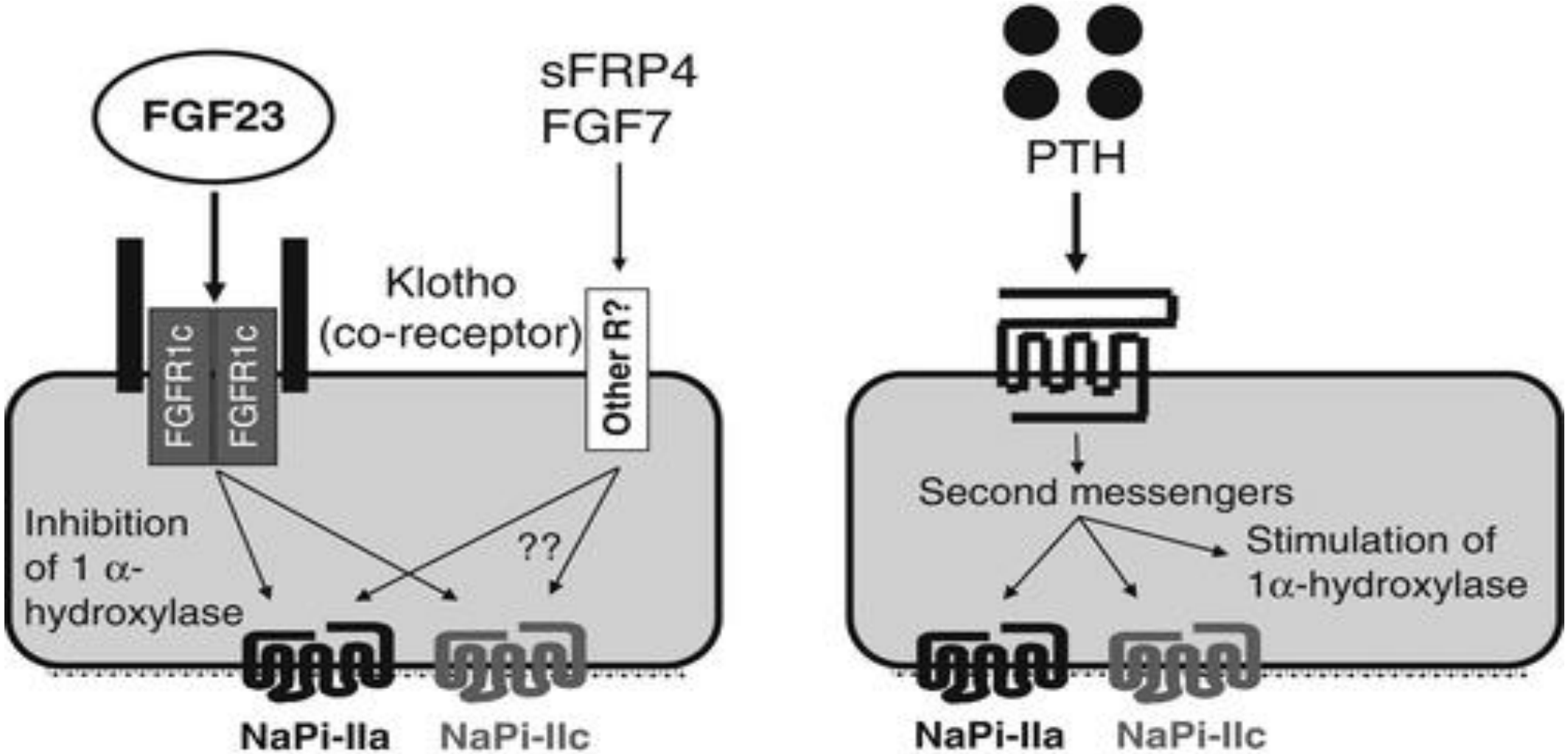
- **before transplantation**, bone loss preferentially affects the **cortical bone** mainly because of **secondary hyperparathyroidism (SHPT).**
- In contrast, There is rapid loss of bone mass in the early **post–transplant** period that frequently affects **trabecular bone** because of decreased bone formation as a result of GC therapy .
- The evolution of **post–transplantation** bone disease is also modified by a variety of post-transplant factors, including the use of immunosuppressive drugs, the degree of graft dysfunction, and disturbances in mineral metabolism, including an increased level of fibroblast growth factor 23, ongoing SHPT, and vitamin D deficiency.
- Progressive **loss of kidney function after transplantation** increases the risk of worsening or de novo development of hyperparathyroidism with active vitamin D deficiency that leads to changes in **bone histomorphometry similar** to those observed before transplantation

- In patients with normal kidney function, the main goal of interplay between Ca ,p,vit D ,PTH & FGF 23 is to preserve serum concentrations of calcium and phosphate, and ultimately bone health.
- PTH synthesis and secretion is influenced by **calcium, phosphate and vitamin D levels.**
- In a functioning kidney, 25-hydroxy vitamin D (25(OH)D) is converted to active 1,25-dihydroxyvitamin D (1,25(OH)D) by 1α-hydroxylase, an enzyme that is upregulated by PTH and inhibited by high FGF-23 levels.
- Active vitamin D can stimulate **gut calcium and phosphate** absorption. Either through increased sodium-phosphate **cotransporter (NaPi-IIb) expression or increased transport via brush-border membrane vesicles**, vitamin D stimulates intestinal phosphate absorption.


1,25(OH)2D3
lumen
blood
VDR
Low Pi diet
active (transcellular)
NPT2b
Pi
3 Na+
High Pi diet
passive (paracellular)

- The majority of filtered phosphate is reabsorbed in the **proximal tubule via the NaPi-IIa and NaPi-IIc cotransporters** .
- PTH and FGF-23 (after binding to the FGF receptor-Klotho complex) interfere with tubular phosphate reabsorption by internalization of NaPi-IIa and NaPi-IIc transporters* .

*Baum M, Schiavi S, Dwarakanath V, Quigley R. Effect of fibroblast growth factor-23 on phosphate transport in proximal tubules. Kidney Int. (2005) 68:1148–53. doi: 10.1111/j.1523-1755.2005.00506.x


FGF23
sFRP4
FGF7
Klotho
(co-receptor)
Other R?
FGFR1c
FGFR1c
Inhibition
of 1 α-
hydroxylase
??
NaPi-IIa
NaPi-IIc
PTH
Second messengers
Stimulation of
1α-hydroxylase
NaPi-IIa
NaPi-IIc

- In patients with chronic kidney disease (CKD) , when GFR falls to less than 60 ml/min, a rise in FGF-23 production by **osteocytes and osteoblasts** is one of the earliest changes .
- **In these patients, serum phosphate is either normal or even slightly lower due to high FGF-23 levels.**
- The exact **stimulus for FGF-23 production** in the bone is not certain, but **1,25(OH)D, dietary phosphate, and reduced clearance** have been reported as potential mechanisms of elevated serum levels *.

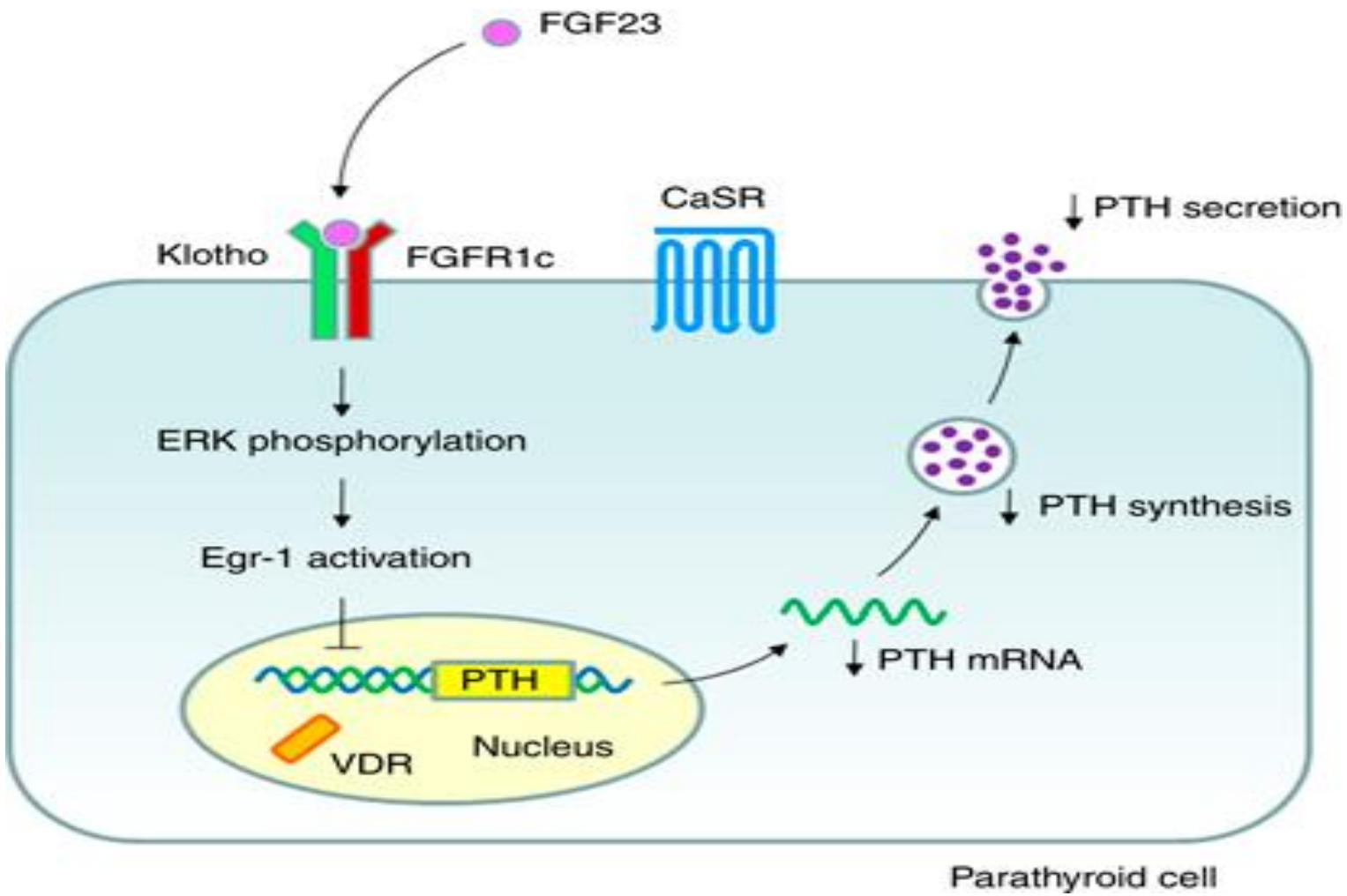
*Nishi H, Nii-Kono T, Nakanishi S, Yamazaki Y, Yamashita T, Fukumoto S, et al. Intravenous calcitriol therapy increases serum concentrations of fibroblast growth factor-23 in dialysis patients with secondary hyperparathyroidism. Nephr Clin Pract. (2005) 101:c94–9. doi: 10.1159/000086347

Klotho

- has been deemed an antifibrotic, antioxidant, and anti-aging protein. Within the domain of MBD, membrane-bound α-klotho has a well-defined role in forming a complex with its obligate co-receptor, FGF-23, and increasing phosphaturia.
- **The distal convoluted tubule is responsible for the majority of α-klotho production .**
- **In addition to the kidney, α-klotho is produced by chief cells of the parathyroid gland .**

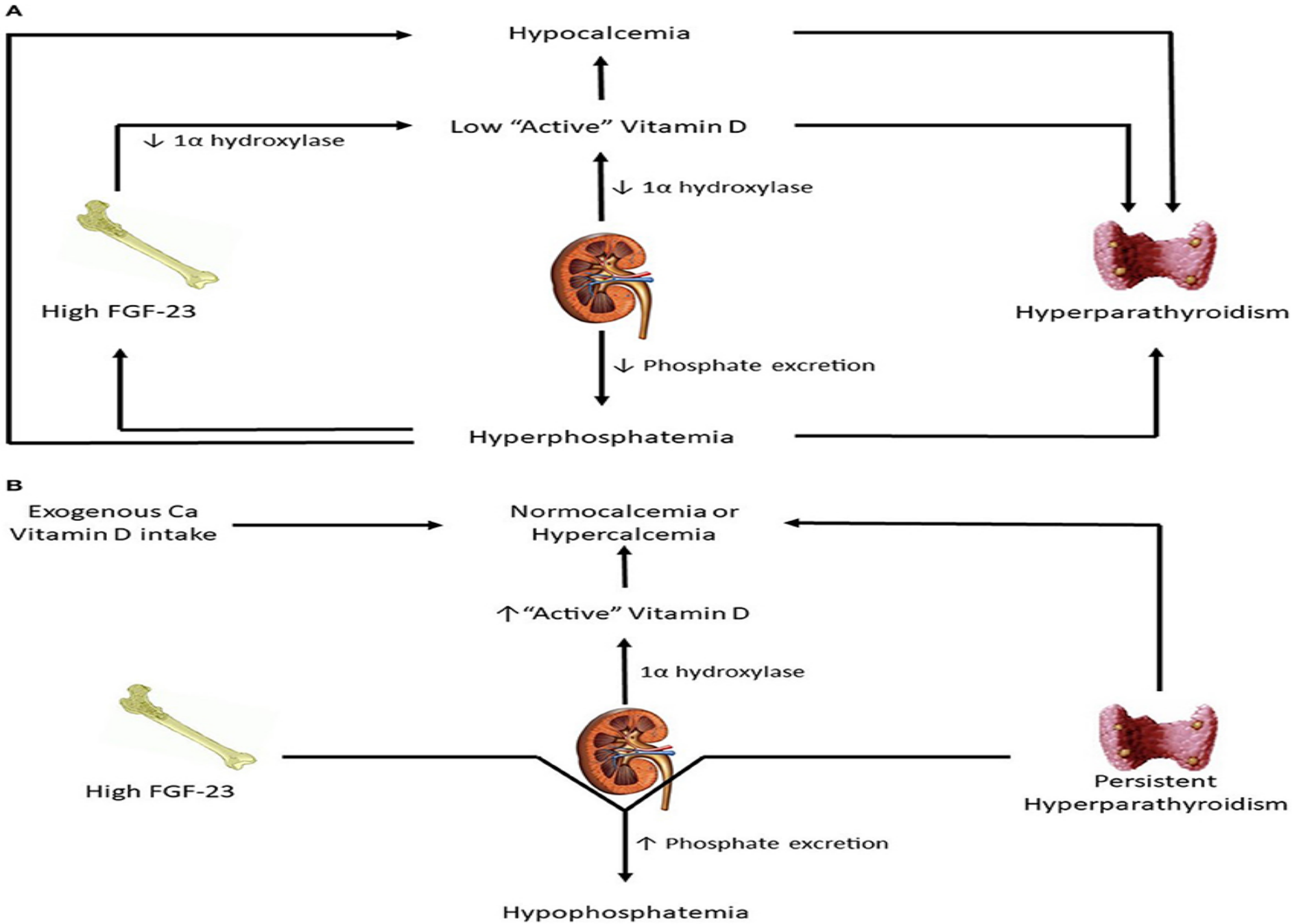
- With FGF receptors also expressed in the **parathyroid gland**, speculation exists on whether α-klotho in conjunction with FGF-23 may **decrease PTH production**, possibly by **increasing expression of both calcium-sensing receptors and vitamin D receptors***.

*Canalejo R, Canalejo A, Martinez-Moreno JM, Rodriguez-Ortiz ME, Estepa JC, Mendoza FJ, et al. FGF23 fails to inhibit uremic parathyroid glands. J Am Soc Nephrol. (2010) 21:1125–35. doi: 10.1681/ASN.2009040427


FGF23
Klotho
FGFR1c
CaSR
PTH secretion
ERK phosphorylation
Egr-1 activation
PTH synthesis
PTH mRNA
PTH
VDR
Nucleus
Parathyroid cell

post-transplant

- with successful transplantation, **GFR is significantly higher**. Immediately post-transplant, circulating levels of **FGF-23 and PTH** are still high.
- As a result, high levels of PTH and FGF-23 result in significant urinary phosphorus losses and **hypophosphatemia** .
- FGF-23 levels drop dramatically at **3 months post-transplantation** and at **1 year** mimic levels seen in CKD patients with comparable eGFR .
- From a vitamin D perspective, a **functioning transplanted kidney and eventual reductions in FGF-23** lead to a gradual increase in **hydroxylation of 25(OH)D** to active 1,25(OH)D, thereby leading to higher gut absorption of calcium and phosphorus.


A
Hypocalcemia
Low "Active" Vitamin D
↓ 1α hydroxylase
↓ 1α hydroxylase
High FGF-23
Hyperparathyroidism
↓ Phosphate excretion
Hyperphosphatemia
B
Exogenous Ca
Vitamin D intake
Normocalcemia or
Hypercalcemia
↑ "Active" Vitamin D
1α hydroxylase
High FGF-23
Persistent
Hyperparathyroidism
↑ Phosphate excretion
Hypophosphatemia

Clinical Spectrum

- Calcium Disorders
  - Hypercalcemia
    - *Hyperparathyroidism*
    - *Exogenous intake of vitamin D and Calcium*
  - Hypocalcemia
    - *Parathyroidectomy: Hungry Bone disease*
- Phosphorus Disorders
  - Hypophosphatemia
    - *High FGF-23 and PTH*
    - *Drugs: Steroids, Sirolimus, Tenofovir, Ferric carboxy-maltose*
  - Hyperphosphatemia
    - *Delayed graft function or CKD in allograft*
- Vitamin D Disorders
  - Hypovitaminosis D
- PTH Disorders
  - Hyperparathyroidism
    - *Polyclonal or monoclonal hyperplasia*
    - *CKD in allograft*
- Osteopenia and Osteoporosis
  - Aging
  - Residual MBD
    - *Hyperparathyroidism*
  - Hypogonadism
  - Medications
    - *Glucocorticoids, proton pump inhibitors, calcineurin inhibitors*
- Osteonecrosis
  - Glucocorticoids

Hypercalcemia

- Hypercalcemia is common after kidney transplantation and has been reported in 11–31% of KTRs within 1 year .
- In some studies, prevalence of hypercalcemia is noted in more than 50% of patients, especially in the subset of patients who had moderate to severe hyperparathyroidism prior to kidney transplantation.
- Severe hypercalcemia can cause **acute kidney injury in the allograft** due to **volume contraction and by reducing perfusion to the allograft by direct vasoconstriction.**
- In the presence of high PTH, phosphaturia and alkaline urine resulting from concurrent use of oral alkali, there is also concern of **nephrocalcinosis.**

drivers of hypercalcemia

- The primary drivers of hypercalcemia are persistent **hyperparathyroidism and high vitamin D levels**.
- In addition to high PTH levels, **resolution of uremia** post-transplant is also associated with a **decrease in skeletal resistance to PTH**.
- In addition to these endogenous changes, most transplant programs use **calcium and vitamin D supplements**, especially when a **steroid** is part of the maintenance immunosuppressive regimen.
- **Rarely**, **acute severe hypercalcemia** can occur in the immediate post-transplant period, requiring emergency parathyroidectomy. Often these patients were **on high doses of cinacalcet** prior to transplantation. **Abrupt discontinuation of cinacalcet post-transplantation** coupled with high PTH and vitamin D levels can lead to acute, severe hypercalcemia.

Work up

- Even though hypercalcemia is multifactorial, most patients have inappropriately high PTH level for the degree of hypercalcemia.
- In such patients, especially in the first few months after transplant, **no further work up** may be needed.
- However, if PTH is appropriately suppressed, **non-PTH related** causes need to be investigated. Similar to evaluation of hypercalcemia in **non-transplant patients**, other etiologies including granulomatous disease, milk-alkali syndrome, malignancies need to be ruled out .
- Low turnover or adynamic bone disease may be associated with hypercalcemia.

Hypocalcemia

- Hypocalcemia is **infrequently** observed after kidney transplantation. Serum calcium levels may decrease initially in **the first week after** transplantation, likely **secondary to a fall in PTH levels and discontinuation of exogenous calcium and vitamin D supplements** . In such patients, hypocalcemia is usually **mild**.

- However, **severe hypocalcemia** and **hungry bone disease** can be seen after **parathyroidectomy surgery**.
- Similarly, patients who had undergone **parathyroidectomy pre-transplant** may be on **high dose parenteral vitamin D supplements**, and usually the **transplant team** and the patient are **unaware** of parenteral medications administered during dialysis. Often these patients are also on calcium-based phosphate binders that are also discontinued post-transplantation. Abrupt cessation of parenteral vitamin D and oral calcium supplements post-transplant may lead to severe hypocalcemia.
- Lastly, a combination of hyperphosphatemia and associated hypocalcemia can be noted in the immediate post-transplant period in patients with **delayed graft function**.

Phosphate Disorders

- Hyperphosphatemia is usually only seen in patients with delayed graft function, or in transplant patients with advanced CKD.

- On the other hand, hypophosphatemia is common in KTRs and occurs **in ~50% of patients**. It most commonly occurs 3–4 weeks after transplantation, especially in patients with immediate graft function and high pre-transplant PTH levels*

*Julian BA, Quarles LD, Niemann KM. Musculoskeletal complications after renal transplantation: pathogenesis and treatment. Am J Kidney Dis. (1992) 19:99–120. doi: 10.1016/S0272-6386(12)70118-X

- It is usually self-limited and serum phosphorus levels begin to normalize within the first few months, correlating with **decline in FGF-23 levels** .However, in a **small fraction of patients, renal phosphate wasting persists** for few months despite normal phosphate levels, and this may be related to persistent hyperparathyroidism .

- Among medications, glucocorticoids can reduce the expression of Na-Pi co-transporters and worsen urinary loss of phosphorus . Steroids can also reduce oral phosphorus absorption in the intestines *.
- Rapamycin may modulate **Klotho expression** through mTORC2 activation and contribute to hypophosphatemia.

*Turner ST, Kiebzak GM, Dousa TP. Mechanism of glucocorticoid effect on renal transport of phosphate. Am J Physiol. (1982) 243:C227–36. doi: 10.1152/ajpcell.1982.243.5.C227

ORIGINAL ARTICLE

Early postkidney transplantation hypophosphatemia

Maryam Ghorbani[1], Shahrzad Ossareh[2]
[1]Department of Internal Medicine, Ziaeian Hospital, Tehran University of Medical Sciences, Tehran, Iran, [2]Department of Medicine, Hasheminejad Kidney Center, Iran University of Medical Sciences, Tehran, Iran

Background: As hypophosphatemia is a common multifactorial problem of kidney transplantation (Tx), this research aimed at studying the frequency of posttransparent hypophosphatemia in the early postkidney Tx period and investigating the risk components associated with the situation. **Materials and Methods:** In this study, 50 renal transplant recipients on the day before (−1) and on days 10 (+10) and 30 (+30) days after kidney Tx were examined for the levels of serum phosphate (Pi). Levels of serum creatinine (Cr), Pi, 25-hydroxyvitamin D (25[OH] D), intact parathyroid hormone (iPTH) and fibroblast growth factor 23 (FGF-23), the 24 h urinary excretion of Pi and Cr, estimated glomerular filtration rate (eGFR), and the ratio of transport maximum of Pi (TMP) to eGFR (TMP/GFR) were evaluated on the same days. **Results:** Hypophosphatemia (serum Pi <2.5 mg/dl) was seen in 0%, 40%, and 42% of the patients on days −1, +10, and +30, respectively. The levels of 25(OH)D and iPTH were not significantly different in patients with and without hypophosphatemia on days +10 and +30. Compared to those with normophosphatemia, pre-Tx FGF-23 level was significantly higher in patients with hypophosphatemia on days +10 and +30, respectively. The regression coefficient of TMP/GFR and Cr was positive on days −1, +10, and +30. The coefficient of pre-Tx FGF-23 on post-Tx serum Pi was negative on days +10 ($P < 0.03$) and +30 ($P < 0.003$), and the coefficient of post-Tx FGF-23 was negative just on day +10 with serum Pi ($P < 0.008$). **Conclusion:** The main causes of post-Tx hypophosphatemia in the multivariate linear analysis were pre-Tx FGF-23 and post-Tx FGF-23 levels on days +10, post-Tx Cr, and TMP/GFR.

In majority of patients, hypophosphatemia is **asymptomatic. Muscle weakness, rhabdomyolysis and hemolysis** do not occur until serum phosphorus concentration is **<1 mg/dL**.

Hypophosphatemia may be associated with a lower risk of **graft failure and cardiovascular mortality**, but not non-cardiovascular or all-cause mortality .

This may likely reflect an underlying association with **elevated FGF-23** levels, which has been demonstrated to be a risk factor for graft loss and mortality*.

*Wolf M, Molnar MZ, Amaral AP, Czira ME, Rudas A, Ujszaszi A, et al. Elevated fibroblast growth factor 23 is a risk factor for kidney transplant loss and mortality. J Am Soc Nephrol. (2011) 22:956–66. doi: 10.1681/ASN.2010080894

Vitamin D Disorders

The majority of KTRs have vitamin D deficiency .When compared with non-transplant controls, KTRs have significantly lower 25(OH)D levels .

Transplant patients frequently have significant vitamin D deficiency in both seasons.

This may be related to avoidance of significant sun exposure and to the use of sunscreen lotions to reduce the risk of skin cancer post-transplant*.

*Ewers B, Gasbjerg A, Moelgaard C, Frederiksen AM, Marckmann P. Vitamin D status in kidney transplant patients: need for intensified routine supplementation. Am J Clin Nutr. (2008) 87:431–7.

From a transplant perspective, low 25(OH)D maybe associated with an increased risk of **all-cause mortality**. **Very low levels** may also be associated with **rapid decline in kidney function**.

Vitamin D deficiency at 3 months post-transplant may be associated with higher risk for significant **interstitial fibrosis and tubular atrophy** at 1 year and as a result, lower GFR *.

However, there are conflicting reports about the link of vitamin D deficiency and increased risk of acute rejection. Also conflicting is the link between **low vitamin D levels and increased risk of cytomegalovirus and BK virus infections .**These observations have not been validated with prospective randomized studies.

Results of the randomized trial (VITA-D) to evaluate the effect of cholecalciferol on graft function, acute rejection rates, and the number and severity of infections within first year of transplantation have not yet been published .

*Bienaime F, Girard D, Anglicheau D, Canaud G, Souberbielle JC, Kreis H,et al. Vitamin D status and outcomes after renal transplantation. J Am Soc Nephrol. (2013) 24:831–41. doi: 10.1681/ASN.2012060614

- **Severe vitamin D deficiency [25(OH)D <10 ng/mL] may be associated with higher risk for posttransplant diabetes* .**
- **A small observational study suggests that the activated vitamin D, paricalcitol, reduces proteinuria in KTRs by reducing inflammation ****.

- Le Fur A, Fournier MC, Gillaizeau F, Masson D, Giral M, Cariou B, etal. Vitamin D deficiency is an independent risk factor for PTDM after kidney transplantation. Transpl Int. (2016) 29:207–15. doi: 10.1111/tri. 12697
- 81. Gonzalez E, Rojas-Rivera J, Polanco N, Morales E, Morales JM, Egido J, et al. Effects of oral paricalcitol on secondary hyperparathyroidism andproteinuria of kidney transplant patients. Transplantation (2013) 95:e49–52.

Hyperparathyroidism

Secondary hyperparathyroidism in advanced CKD results from multiple stimuli, including hyperphosphatemia, hypocalcemia, low 1,25(OH)D levels, and skeletal resistance to PTH.

These factors result in continuous stimulation of PTH synthesis and secretion. **Parathyroid hyperplasia** that ensues is initially **diffuse and polyclonal**, and still responds to vitamin D therapy and cinacalcet.

However, with time, there is **down regulation of vitamin D receptors and calcium-sensing receptors** in the parathyroid tissue, and hyperplasia often becomes **monoclonal or nodular in nature.**

In such patients, PTH synthesis and secretion become **autonomous** with minimal response to therapeutic agents and is often associated **with hypercalcemia.**

When measured by ultrasound, diffuse polyclonal hyperplastic glands are significantly smaller than nodular monoclonal glands.

- With successful transplantation and higher GFR,most of these stimuli of parathyroid hyperplasia abate. This often leads to a gradual decline in PTH concentrations. Unlike FGF-23 levels that precipitously decline post-transplant, the fall in PTH is more gradual.

- It has been reported that 25 to>80%of patients still have inappropriately high PTH beyond 1-year post transplant *.
- Pre-transplant cinacalcet use, development of nodular hyperplasia, and dialysis vintage are associated with high PTH levels after transplant ,while use of vitamin D pre-transplant appears to be protective**.

*Yakupoglu HY, Corsenca A, Wahl P, Wuthrich RP, Ambuhl PM. Posttransplant acidosis and associated disorders of mineral metabolism in patients with a renal graft. Transplantation (2007) 84:1151–7. doi: 10.1097

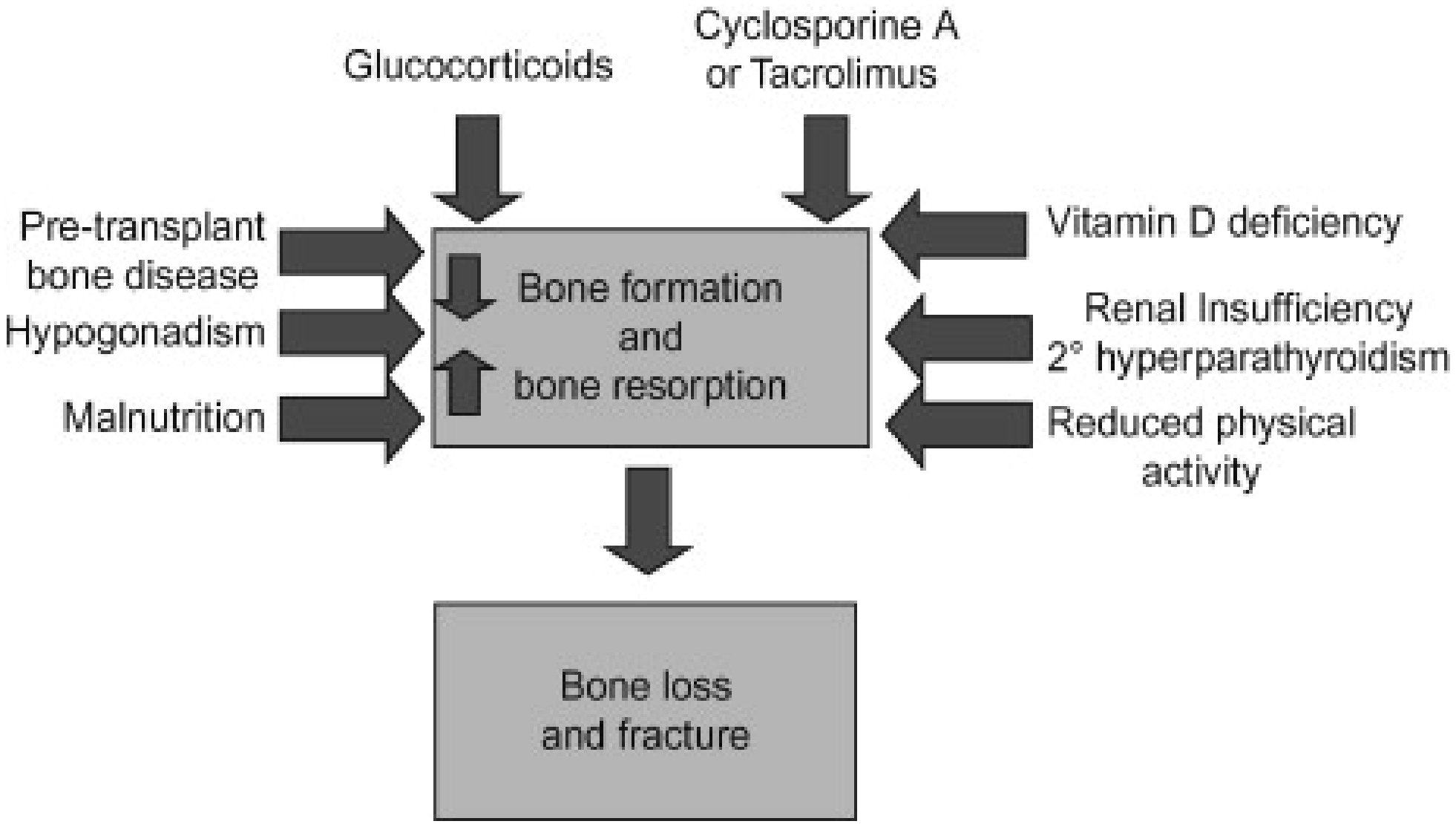
**Koch Nogueira PC, David L, Cochat P. Evolution of secondary hyperparathyroidism after renal transplantation. Pediatr Nephrol. (2000)

Osteopenia and Osteoporosis

- Osteopenia and osteoporosis are conditions highlighted by **microarchitectural changes that result in reduced bone mass and increased skeletal fragility.**
- As in the general population, age, race, ethnicity, weight, diabetes mellitus, tobacco use, and menopausal status influence osteoporotic risk.
- After transplantation, several other factors including residual MBD, glucocorticoids, hypomagnesemia, and hypogonadism play a role in bone loss.
- **Transplant medications modify osteoprotegerin and the receptor activator of nuclear factor-kB ligand (RANKL), potent mediators of the bone remodeling process.**
- Through regulation of the RANKL system, **glucocorticoids** decrease osteoblast proliferation and differentiation, while promoting osteoclastogenesis . Additionally, they decrease intestinal calcium absorption and increase urinary calcium loss*.
- The **rate of bone loss** is greatest in the **first 3–6 months of steroid** use when assessed by bone mineral density (BMD) Even when these reductions in bone mass are not evident, **low dose glucocorticoid** use is still associated with reduced bone strength**.

*Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid induced osteoporosis: pathophysiology and therapy. Osteoporosis Int. (2007) 18:1319–28. doi: 10.1007/s00198-007-0394-0

**Laan RF, van Riel PL, van de Putte LB, van Erning LJ, van'tHof MA, Lemmens JA. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study. Ann Int Med. (1993) 119:963–8.


Glucocorticoids
Cyclosporine A
or Tacrolimus
Pre-transplant
bone disease
Hypogonadism
Malnutrition
Bone formation
and
bone resorption
Vitamin D deficiency
Renal Insufficiency
2° hyperparathyroidism
Reduced physical
activity
Bone loss
and fracture

- Both **tacrolimus and sirolimus** can increase **osteoblast apoptosis**.
- **Hypomagnesemia**, possibly by **stimulating PTH secretion** and osteoclastogenesis while inhibiting osteoblast proliferation.Magnesium deficiency is a common complication for KTRs and is often related to medications, including **calcineurin inhibitors, proton pump inhibitors, and pentamidine.**
- **Gonadal hormones play a significant role in achieving peak bone mass, and hypogonadism is associated with bone loss and low BMD.**
- **40% of ESRD patients have testosterone deficiency and sex hormone production can improve significantly within the first 3 months post-transplantation in patients younger than 50 years old. Despite resolution of uremia, chronic use of glucocorticoids may decrease gonadal hormones in KTRs*.**
- **Recently, proton pump inhibitors have been associated with hip fractures among KTRs ,reduced cation absorption**.**

*Reinhardt W, Kubber H, Dolff S, Benson S, Fuhrer D, Tan S. Rapid recovery of hypogonadism in male patients with end stage renal disease after renal transplantation. Endocrine (2018) 60:159–66.

**Lenihan CR, Sukumaran Nair S, Vangala C, Ramanathan V, Montez-Rath ME, Winkelmayer WC. Proton pump inhibitor use and risk of hip fracture in kidney transplant recipients. Am J Kidney Dis. (2017) 69:595–601. 10.1053/j.ajkd.2016.09.019.

Risks factors associated with post–transplantation bone loss and fractures

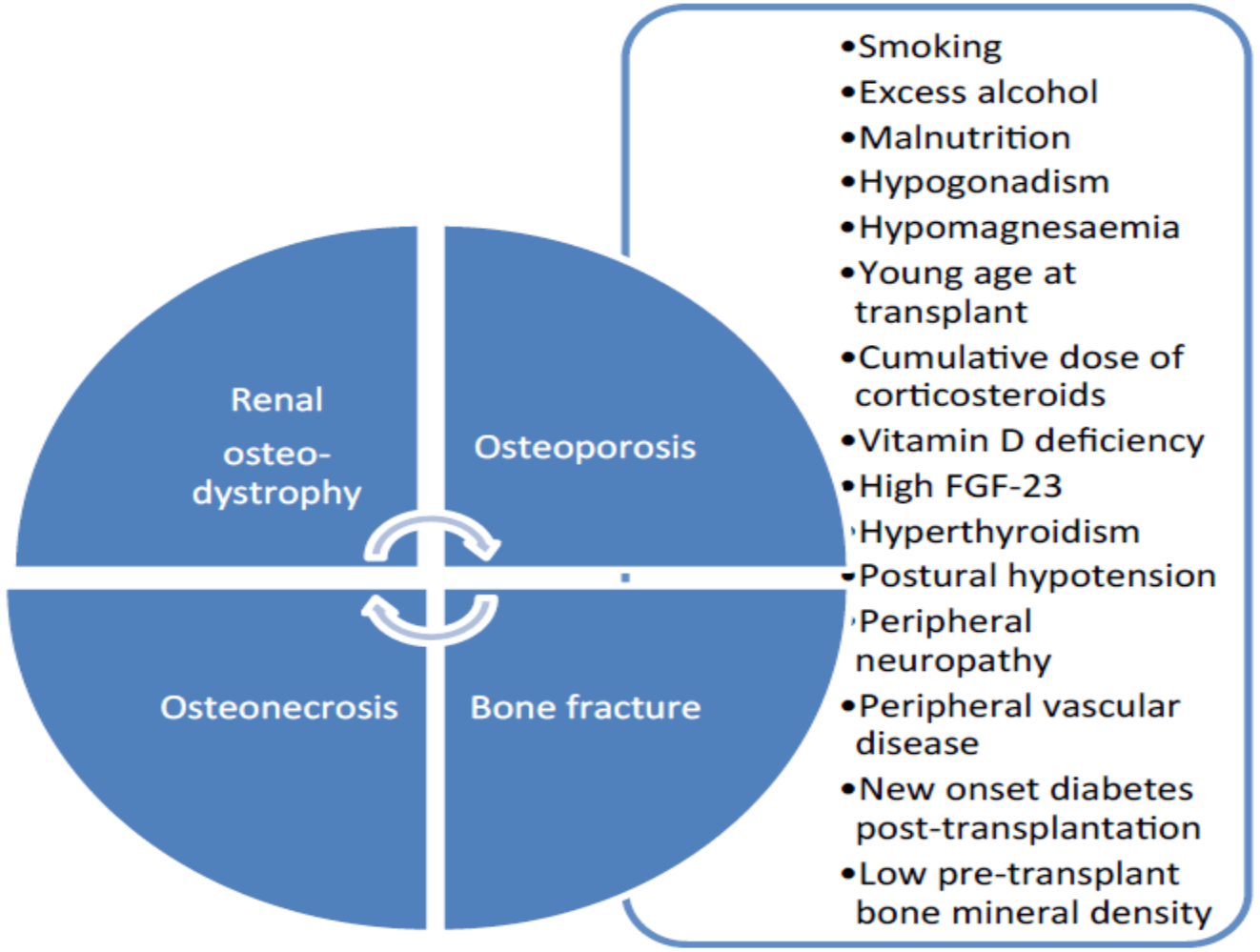


Figure 1: Risk factors for osteoporosis and fractures in renal transplant recipients.

Osteonecrosis

- Osteonecrosis or avascular bone necrosis, a pathological condition characterized by **bone death**, has a strong association with glucocorticoid use. Prevalence has been reported to be between 3-40% in different studies* .
- However, with introduction of calcineurin inhibitors and consequent reduction in steroid doses, the incidence of osteonecrosis has declined significantly** .
- While the exact pathogenesis remains unclear, possible mechanisms include steroid-induced **decrease in vascular endothelial growth factor**, alterations in **circulating lipids with resultant fat emboli**, **increased apoptosis of osteoblasts, osteocytes and endothelial cells**, **adipogenesis**, **procoagulant state**, **modulation of vasoactive mediators**, and **elevated intraosseous pressure**, which eventually lead to ischemia and necrosis .
- The hips, knees, and shoulders are the most commonly affected sites.

*Nayagam LS, Rajan SG, Khandelwal N, Sen R, Kohli HS, Sud K, et al. . Bilateral femoral capital avascular necrosis in a renal transplant recipient on tacrolimus-based immunosuppression. Nephrol Dial Transplant (2005) 20:2262–4. 10.1093/ndt/gfh982

**Sakai T, Sugano N, Kokado Y, Takahara S, Ohzono K, Yoshikawa H. Tacrolimus may be associated with lower osteonecrosis rates after renal transplantation. Clin Orthop Relat Res. 2003:163–70. 10.1097/01.blo.0000093908.26658.df

Managemen of osteonecrosis

- **Prevention**, **early diagnosis**, and **slowing the progression** of osteonecrosis is key, as there is no proven therapy, especially for advanced disease.
- This includes **limiting steroid use**, and avoiding other risk factors, including **alcohol use and smoking.**
- Surgical options for symptomatic patients with progressive early stage osteonecrosis include **core decompression, osteotomy, and bone grafting**.
- When bone collapse has already occurred, hemiarthroplasty or total-hip arthroplasty may be offered.
- Recently, surgeons have considered combining core decompression with **stem cell-based** (implantation of autologous bone marrow concentrate or mesenchymal stem cell) and **growth factor-based** (bone morphogenic proteins, vascular endothelial growth factor) regenerative therapies*.
- * Rackwitz L, Eden L, Reppenhagen S, Reichert JC, Jakob F, Walles H, et al. . Stem cell- and growth factor-based regenerative therapies for avascular necrosis of the femoral head. Stem Cell Res Ther. (2012) 3:7. 10.1186/scrt9

Evaluation of MBD post-transplant

- Biochemical assessment:
- KDIGO 2017 guideline update recommends that serum calcium and phosphorus levels be measured at least weekly in the immediate post-kidney transplant period until stable (graded 1B) .
- After the immediate post-kidney transplant period, the frequency of monitoring serum calcium and phosphorus levels can be based on the rate of progression of CKD, the presence and magnitude of abnormalities, and whether the patient is receiving treatments for CKD-MBD (not graded).
- monitoring intervals include: (1) every 6–12 months in CKD stages 1-3T; (2) every 3–6 months in CKD stage 4T; and (3) every 1–3 months in CKD stage 5T.

- The KDIGO 2017 guideline update suggests that a baseline **25(OH)D** level might be measured in the **immediate post-transplant** period, and repeated testing should be determined by baseline values and interventions .
- It also recommends measuring a **baseline PTH** level in the immediate post-transplant period and subsequent monitoring be based on the rate of progression of CKD, baseline level, and whether the patient is receiving treatments for CKD-MBD (not graded).
- Recommended monitoring intervals include: (1) variable in CKD stages 1-3T, depending on baseline level and CKD progression; (2) every 6–12 months in CKD stage 4T; and (3) every 3–6 months in CKD stage 5T

Evaluating fracture risk

- **Dual energy X-ray absorptiometry bone mineral density (DXA BMD):**
- The use of DXA to predict fracture risk in KTRs remains a **challenge.**
- Limitations include: (1) inability to distinguish between **cortical and trabecular bone**, which are differentially affected in secondary hyperparathyroidism; (2) confounding **signals from concomitant vascular calcification**; and (3) observations that **glucocorticoid-induced fractures occur at higher BMD values** than in patients with non-glucocorticoid-induced osteoporosis .
- A study showed that KTRs with **hip bone** osteopenia (HR 2.7; 95% CI 1.6–4.6) and osteoporosis (HR 3.5, 95% CI 1.8–6.4) noted on DXA have an increased risk of fracture; the predictive value of DXA BMD results in the **lumbar spine** was much less certain *
- Furthermore, a recent meta-analysis and several prospective studies in adults with CKD G3a to G5D stages showed that DXA BMD, especially at the **total hip region,** predicts fractures across the spectrum of CKD **
- Based on these data, KDIGO guidelines 2017 update recommends BMD testing in patients with CKD G1T-G5T with risk factors for osteoporosis, if results will alter therapy (grade 2C) ***
- With the overwhelming majority of KTRs **having additional risk factors** (steroid use, age, diabetes, etc.) for osteoporosis, screening DXA scans are ordered at **months 3 and 15** at our institution.

*Akaberi S, Simonsen O, Lindergard B, Nyberg G. Can DXA predict fractures in renal transplant patients? Am J Transplant. (2008) 8:2647–51. 10.1111/j.1600-6143.2008.02423.x

**Bucur RC, Panjwani DD, Turner L, Rader T, West SL, Jamal SA. Low bone mineral density and fractures in stages 3-5 CKD: an updated systematic review and meta-analysis. Osteoporos Int. (2015) 26:449–58. 10.1007/s00198-014-2813-3

***Isakova T, Nickolas TL, Denburg M, Yarlagadda S, Weiner DE, Gutierrez OM, et al. . KDOQI US commentary on the 2017 KDIGO clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Am J Kidney Dis. (2017) 70:737–51. 10.1053/j.ajkd.2017.07.019

Fracture risk assessment tool (FRAX)

- The World Health Organization's FRAX Tool is used commonly in the general population to predict the 10-year probability of a major osteoporotic fracture.
- It utilizes an algorithm that includes age, sex, and several clinical risk factors for fracture, including parental hip fracture, previous fragility fracture, rheumatoid arthritis, current smoking, secondary osteoporosis, low body mass index (BMI < 19 kg/m2), prolonged glucocorticoid use, and excessive alcohol intake.
- The FRAX score does not require bone densitometry data to predict fracture risk, making it an attractive clinical tool.
- However, the etiology of transplant bone disease is multifactorial, and pathology is widely variable. Therefore, factors in the FRAX algorithm that are associated with fracture risk in the general population may not accurately predict fractures in KTRs.

Evaluation/imaging beyond DXA

- **High-resolution peripheral quantitative computed tomography** provides a mechanism for understanding density and microarchitecture of cortical and trabecular regions separately .
- Peripheral examination ignores the two most common osteoporotic fracture sites: proximal femur and spine.
- Bone architecture associated with kidney disease is not uniform and **radial evaluation** may not reflect the turnover, density, and strength present at the hip.
- Currently, this technology largely exists for research purposes, as the above barriers, along with cost, must be overcome before broader clinical application materializes.

Bone biopsy

- Bone biopsy is an informative diagnostic procedure to evaluate bone abnormalities in patients with kidney disease. To interpret bone biopsy results better, **TMV classification** was developed using three histologic descriptors assessed by bone **histomorphometry**; bone **turnover (T), mineralization (M) and volume (V).** While mineralization is classified as normal or abnormal, turnover and volume can be classified as low, normal or high.

- Compared to older studies that showed higher prevalence of mixed uremic osteodystrophy in KTRs*, recent studies have shown that osteitis fibrosa is more common** .
- However, in a more recent study, bone turnover was normal and bone **mineralization was delayed** in the majority of patients ***.

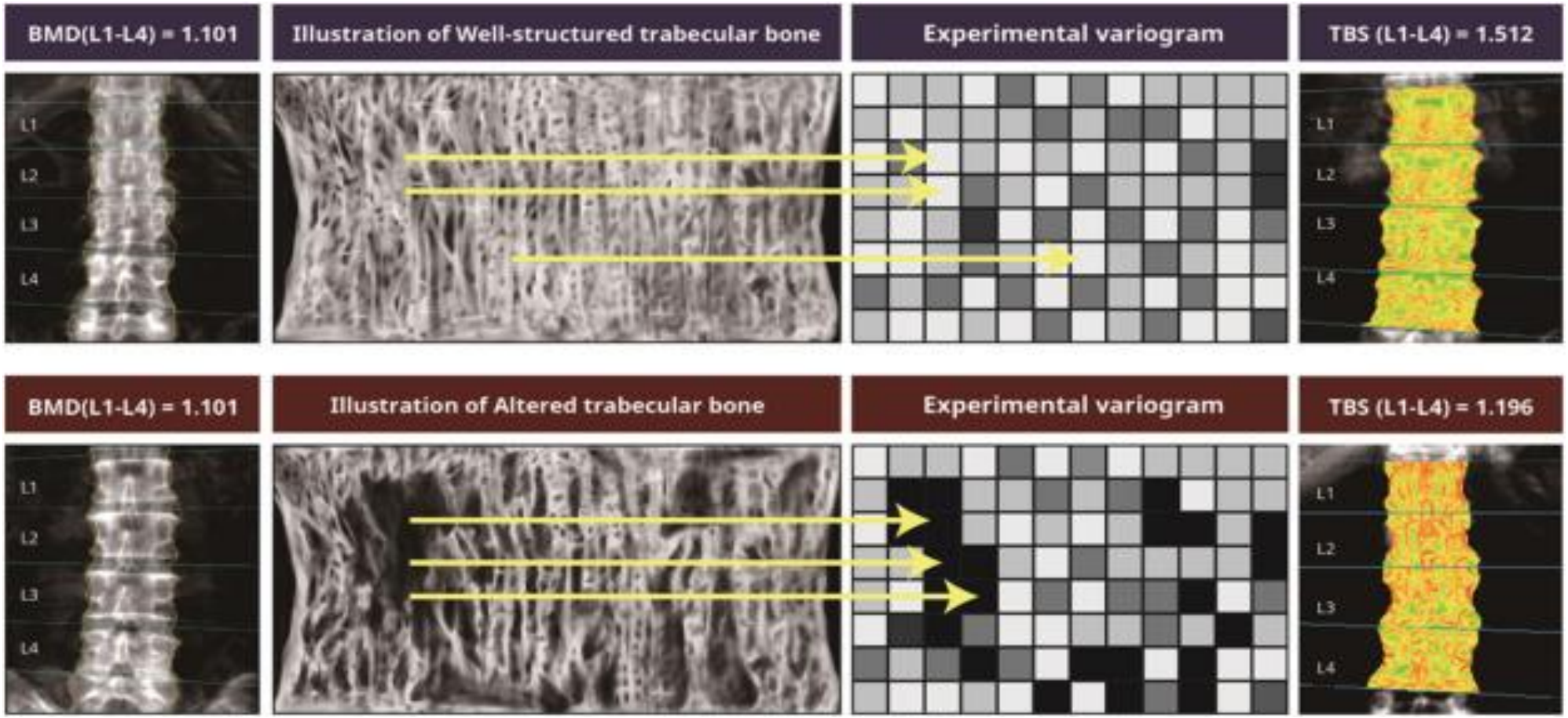
*Cueto-Manzano AM, Konel S, Hutchison AJ, Crowley V, France MW, Freemont AJ, et al. . Bone loss in long-term renal transplantation: histopathology and densitometry analysis. Kidney Int. (1999) 55:2021–9. 10.1046/j.1523-1755.1999.00445.x

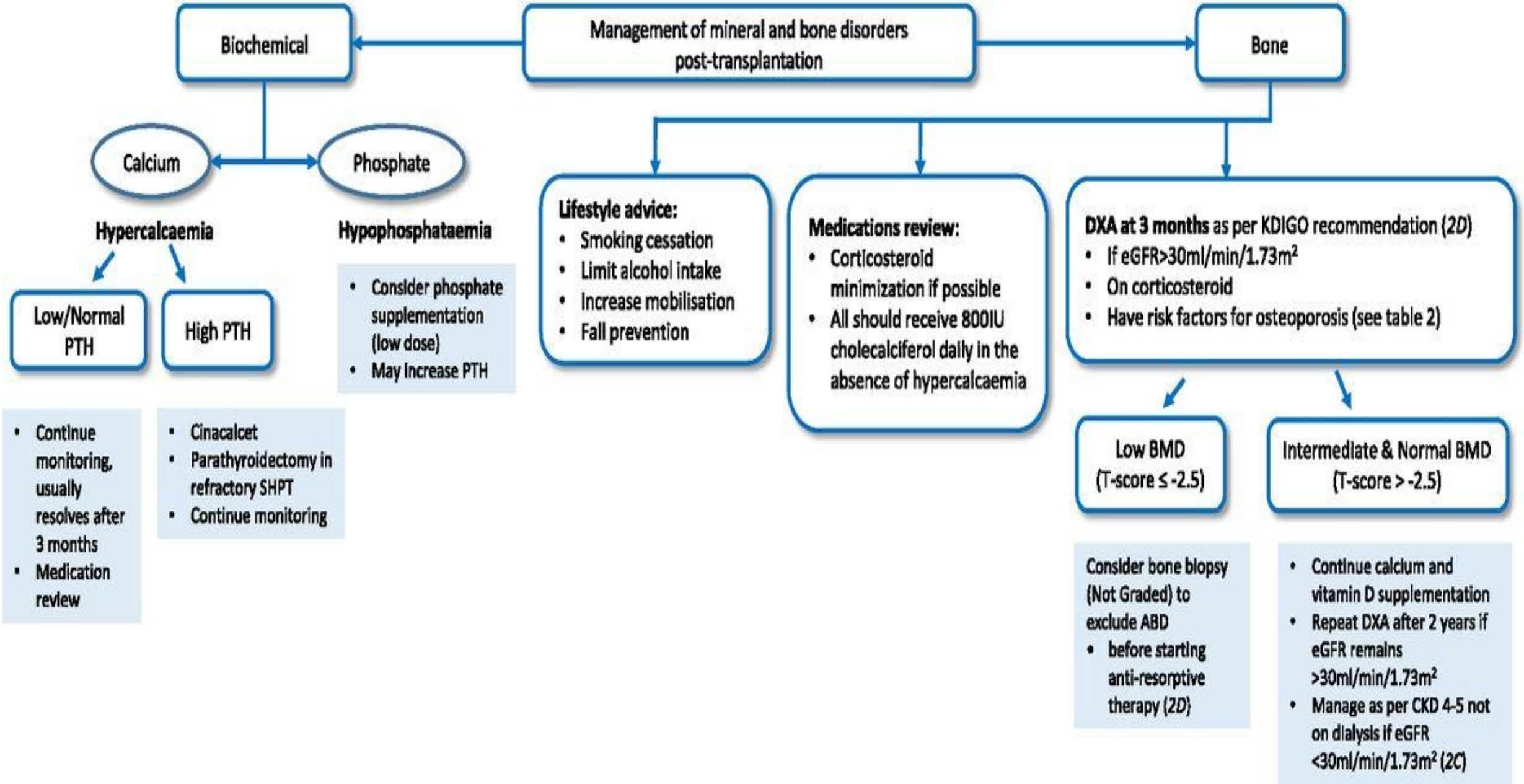
**Lehmann G, Ott U, Stein G, Steiner T, Wolf G. Renal osteodystrophy after successful renal transplantation: a histomorphometric analysis in 57 patients. Transplant Proceed. (2007) 39:3153–8. 10.1016/j.transproceed.2007.10.001

***Neves CL, dos Reis LM, Batista DG, Custodio MR, Graciolli FG, Martin Rde C, et al. . Persistence of bone and mineral disorders 2 years after successful kidney transplantation. Transplantation (2013) 96:290–6. 10.1097/TP.0b013e3182985468

- A novel parameter for describing microarchitecture, **trabecular bone score**, may provide a potential method for examining bone quality and strength through **gray-scale variograms of the spine** image available from a **DXA** *.
- In KTRs, trabecular bone scores are associated with fractures independent of a Fracture Risk Assessment score including BMD. These scores were also predictive of worsening trabecular microarchitecture and failure load as measured by high-resolution peripheral quantitative computed tomography and have already been incorporated into the World Health Organizations FRAX tool. This additional assessment should warrant more attention given its simplicity and accessibility.

*Harvey NC, Gluer CC, Binkley N, McCloskey EV, Brandi ML, Cooper C, et al. . Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice. Bone (2015) 78:216–24. 10.1016/j.bone.2015.05.016


BMD(L1-L4) = 1.101
Illustration of Well-structured trabecular bone
Experimental variogram
TBS (L1-L4) = 1.512
L1
L2
L3
L4
BMD(L1-L4) = 1.101
Illustration of Altered trabecular bone
Experimental variogram
TBS (L1-L4) = 1.196
L1
L2
L3
L4


Management of mineral and bone disorders post-transplantation
Biochemical
Bone
Calcium
Phosphate
Hypercalcaemia
Hypophosphataemia
Low/Normal PTH
High PTH
• Continue monitoring, usually resolves after 3 months
• Medication review
• Cinacalcet
• Parathyroidectomy in refractory SHPT
• Continue monitoring
• Consider phosphate supplementation (low dose)
• May increase PTH
Lifestyle advice:
• Smoking cessation
• Limit alcohol intake
• Increase mobilisation
• Fall prevention
Medications review:
• Corticosteroid minimization if possible
• All should receive 800IU cholecalciferol daily in the absence of hypercalcaemia
DXA at 3 months as per KDIGO recommendation (2D)
• If eGFR>30ml/min/1.73m²
• On corticosteroid
• Have risk factors for osteoporosis (see table 2)
Low BMD (T-score ≤ -2.5)
Intermediate & Normal BMD (T-score > -2.5)
Consider bone biopsy (Not Graded) to exclude ABD
• before starting anti-resorptive therapy (2D)
• Continue calcium and vitamin D supplementation
• Repeat DXA after 2 years if eGFR remains >30ml/min/1.73m²
• Manage as per CKD 4-5 not on dialysis if eGFR <30ml/min/1.73m² (2C)

Phosphate supplementation

- Due to ongoing urinary losses in the immediate post-transplant period, it is often difficult to achieve and maintain normal serum phosphate levels with oral replacements.
- Oral supplements (**oral sodium-potassium phosphate tablet and powder**) are started when serum phosphate level is **<2 mg/dL** with a goal to maintain serum level around 2 mg/dL. It is recommended not to elevate serum level to normal range for fear of exacerbating hyperparathyroid state. There is also concern of nephrocalcinosis with aggressive replacement, especially in the presence of hyperparathyroidism, simultaneous use of cinacalcet, and oral alkali.
- Each 250 mg tablet contains around 8 mmol of phosphate.
- Neutral phosphate salt supplementation, in addition to correcting hypophosphatemia, has been shown to increase **muscle ATP and phosphodiester content** without affecting other mineral metabolism and has been shown to **improve renal acid excretion** .
- In addition to pharmacologic supplementation, it is recommended high phosphorus containing diets.
- studies recommend patients to liberalize intake of skim milk every day and other dairy products; **480 mL of skim milk contains 15 mmol of phosphate**. If skim milk cannot be tolerated, a less favorable alternative would be temporary intake of diet **cola drinks**.

TREATMENT OF HYPERCACEMIA

- In majority of patients, hypercalcemia is gradual, asymptomatic, and can be medically managed.
- In patients with mild hypercalcemia, we encourage adequate fluid intake and avoidance of medications that can independently increase serum calcium levels, such as thiazide diuretics and calcium supplements.
- If vitamin D replete, vitamin D supplements should be discontinued.
- If hypercalcemia persists despite these measures, and if PTH level is persistently high, cinacalcet can be started temporarily and dose titrated .
- If cinacalcet cannot be continued for financial reasons or intolerance to the drug, then subtotal parathyroidectomy should be considered to treat tertiary hyperparathyroidism* .
- Since involution of hyperplastic parathyroid glands and a resultant decline in PTH concentration occur over a year, many transplant physicians prefer to wait for at least a year after kidney transplantation before proceeding to surgery, provided there is no graft dysfunction related to hypercalcemia.
- Also, treatment of osteoporosis with bisphosphonates and denosumab may improve serum calcium levels.

*Lou I, Schneider DF, Leverson G, Foley D, Sippel R, Chen H. Parathyroidectomy is underused in patients with tertiary hyperparathyroidism after renal transplantation. Surgery (2016) 159:172–9. doi: 10.1016/j.surg.2015.08.039

Calcium and vitamin D supplementation

- While most patients with mild hypocalcemia can be managed with oral calcium supplements, patients with hungry-bone disease and severe hypocalcemia need high-dose activated vitamin D such as calcitriol or paricalcitol, along with parenteral calcium infusions followed by high-dose oral calcium supplements.
- It is recommended the use of **calcium and cholecalciferol in all kidney transplant patients with normal serum calcium**. Especially when steroids are given, administration of vitamin D **improves GI calcium absorption**.
- Most agree the use of adequate dose of vitamin D to correct vitamin D deficiency and **maintain serum 25(OH)D level of >30 ng/mL**. The KDIGO 2009 guidelines suggest Vitamin D deficiency should be corrected as recommended for the general population (graded 2C) .
- If the patient develops hypercalcemia, vitamin D supplementation should be discontinued until serum calcium normalizes.

paricalcitol

- Active vitamin D supplementation has been used successfully to treat secondary hyperparathyroidism in KTRs in much the same way that it is utilized in patients with CKD.
- In fact, paricalcitol, whether given intravenously or orally, has even been shown to be **more effective than cinacalcet in reaching goal PTH** and reducing markers of bone turnover .
- Both the use of calcitriol and paricalcitol have resulted in improved BMD while reduced markers of inflammation have been found among KTRs that are administered paricalcitol .
- Paricalcitol has also demonstrated variable results regarding **proteinuria reduction in KTRs** and has been touted as having an **anti-fibrotic** advantage over calcitriol in mice studies .**Despite these benefits**, active vitamin D supplementation results in relative **increases in FGF-23**, the downstream effects of which are still not completely understood.

Cinacalcet

- In KTRs with hyperparathyroidism and hypercalcemia, **cinacalcet** reduces PTH levels and as a result, improves serum calcium and serum phosphate levels .
- Regression of **parathyroid hyperplasia** has been documented .
- Some studies have shown improvement in **bone mineral density**, especially at the **hip** level *. **However, there are no randomized controlled trials that have shown improvement in patient survival, much less fractures.**
- Due to **cinacalcet's effect on renal sodium handling**, some studies have shown improvement in blood pressure **.
- However, these potential benefits must be balanced by the commonly **encountered gastrointestinal intolerance and higher urinary fractional excretion of calcium** and **hypercalciuria .**
- In fact, reports **of allograft nephrocalcinosis** *** and consequent **graft failure** have been reported. Despite this risk, studies **demonstrating no change in allograft function** with long-term use of cinacalcet exist ****.

*Bergua C, Torregrosa JV, Fuster D, Gutierrez-Dalmau A, Oppenheimer F, Campistol JM. Effect of cinacalcet on hypercalcemia and bone mineral density in renal transplanted patients with secondary hyperparathyroidism. Transplantation (2008) 86:413–7. 10.1097/TP.0b013e31817c13e1

**Zitt E, Woess E, Mayer G, Lhotta K. Effect of cinacalcet on renal electrolyte handling and systemic arterial blood pressure in kidney transplant patients with persistent hyperparathyroidism. Transplantation (2011) 92:883–9. 10.1097/TP.0b013e31822d87e8

***Peng LW, Logan JL, James SH, Scott KM, Lien YH. Cinacalcet-associated graft dysfunction and nephrocalcinosis in a kidney transplant recipient. Am J Med. (2007) 120:e7–9. 10.1016/j.amjmed.2005.09.041

****Cohen JB, Gordon CE, Balk EM, Francis JM. Cinacalcet for the treatment of hyperparathyroidism in kidney transplant recipients: a systematic review and meta-analysis. Transplantation (2012) 94:1041–8. 10.1097/TP.0b013e31826c3968

- There may be drug-drug interaction between cinacalcet and tacrolimus; when given together, cinacalcet may reduce tacrolimus concentration .
- Cinacalcet does not seem to interfere with pharmacokinetics of cyclosporine or mycophenolate .
- It is also important to note that co-administration of a potent CYP3A4 inhibitor (e.g., protease inhibitors, itraconazole, diltiazem etc.) may increase serum levels of cinacalcet since the drug is partially metabolized by that pathway. Serum calcium should be closely monitored in such patients.
- In addition, cinacalcet is also a potent inhibitor of CYP2D6 pathway. When cinacalcet is combined with other potent inhibitors of CYP2D6 pathway like SSRI antidepressants (fluoxetine, paroxetine), inhibition of this metabolic pathway can be profound. In such patients, doses of medications that are metabolized by CYP2D6 pathway (metoprolol, carvedilol, tricyclic antidepressants, flecainide etc.) should be adjusted to avoid toxicity.

cinacalcet

In the post-transplant setting, cinacalcet is primarily used for the management of **severe hypercalcemia associated with tertiary hyperparathyroidism**. Since cinacalcet is not FDA approved in KTRs, most programs use the drug only in patients with **refractory and severe hypercalcemia (corrected serum calcium >11 mg/dL).**

There are no clear guidelines for the use of this drug. Thus, while the benefit for serum calcium reduction and perhaps BMD improvement is evident in tertiary hyperparathyroidism, its utility in persistent hyperparathyroidism without hypercalcemia or de novo hyperparathyroidism is less certain. With unclear targets, particularly as graft function worsens, one risks over-suppression and potential adynamic bone disease.

Anti-resorptive agents: bisphosphonates

- With a very low level of evidence, the KDIGO guideline on transplant suggests considering bisphosphonate treatment within the **first 12 months of transplant** *.In particular, the guideline highlights the utility of **bone biopsy** if considering bisphosphonate therapy. However, excluding adynamic bone disease with this antiquated procedure **is not feasible** in most transplant centers. Thus, care is reduced to estimating bone turnover rate in conjunction with BMD to determine the utility of bisphosphonates. If the risk of adynamic bone disease can be eliminated with **elevated markers of bone turnover such as bone-specific alkaline phosphatase**, KTRs with high risk and **reduced BMD** should be considered for bisphosphonate therapy.

*Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. (2009) 9(Suppl. 3):S1–155. 10.1111/j.1600-6143.2009.02834.x

- **After the first-year post-transplant**, insufficient evidence exists to guide whether bisphosphonate therapy should be continued. KTRs should be re-evaluated in terms of their glucocorticoid dose and repeat DXA.
- More specifically, an alternative anti-resorptive medication, teriparatide, a **PTH analogue**, may have a **role in adynamic bone disease**, which is characterized by PTH resistance and relative PTH deficiency. Teriparatide has been successfully used to improve BMD in patients with glucocorticoid-induced osteoporosis .

- **Denosumab, a RANKL inhibitor** presents an attractive alternative, particularly in patients with **low GFR**. These patients require **close monitoring for hypocalcemia**. Much like bisphosphonate use, BMD parameters seem to improve, but no evidence exists for changes in fracture risk .

Parathyroidectomy

- A recent retrospective study of 913 patients at a single center that underwent kidney transplantation concluded that **levels greater than 6 times normal** were associated with graft failure, and pre-transplant PTX decreased the risk of allograft failure*.

Even though high **PTH levels (>500 pg/mL) and serum calcium level (>9.5 mg/dL)** are risk factors for needed PTX post-transplant, enough time should be given for spontaneous **regression of gland hyperplasia** if surgery is planned post-transplant. Post-transplant PTH levels appear to fall rapidly in functional allografts **3-6 months post-operatively,** and then follow a more gradual **decline that plateaus at 1 year .**

It follows then that referral for operative intervention for persistent disease should be delayed at least 3 months, but not extend past 1 year due to cumulative risk of cardiac, bone and graft complications associated with high PTH and calcium levels.

Data regarding the effect of parathyroidectomy on renal allograft function is conflicting, with some studies suggesting decreasing function post intervention, while others found no significant long-term difference .**

- Current reports suggest a less extreme approach, including less-than-subtotal parathyroidectomy, may achieve similar therapeutic goals ***.

*Parathyroidectomy prior to kidney transplant decreases graft failure. Callender GG, Malinowski J, Javid M, Zhang Y, Huang H, Quinn CE, Carling T, Tomlin R, Smith JD; Kulkarni Surgery. 2017 Jan; 161(1):44-50

**Parathyroidectomy is underused in patients with tertiary hyperparathyroidism after renal transplantation. Lou I, Schneider DF, Leverson G, Foley D, Sippel R, Chen H

Surgery. 2016 Jan; 159(1):172-9.

*** Surgical management of secondary hyperparathyroidism in chronic kidney disease--a consensus report of the European Society of Endocrine Surgeons. Lorenz K, Bartsch DK, Sancho JJ, Guigard S, Triponez FLangenbecks Arch Surg. 2015 Dec; 400(8):907-27.

Thanks for attention