Mineral Bone Disorders After Kidney Transplantation

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Introduction

- After kidney transplantation, mineral and bone disorders are associated with higher risk of fractures and consequent morbidity and mortality.
- Bone disease after kidney transplantation is highly prevalent in patients living with a kidney transplant and is associated with high rates of **hip fractures**, which are associated with increased healthcare costs, morbidity and mortality .
- Post-transplant bone disease (PTBD) is used to describe a variety of bone diseases diagnosed after kidney transplantation, including **renal osteodystrophy, osteoporosis, bone fracture and osteonecrosis**
-

Pathophysiology

- The pathogenesis of osteoporosis begins prior to transplantation.
- This is then followed by post-transplantation changes in physiology influenced by medication.
- the **persistence of secondary and tertiary hyperparathyroidism**, renal osteodystrophy, hyperparathyroidism,, relative choleciferol deficiency and a high level of fibroblast growth factor-23 (FGF-23).

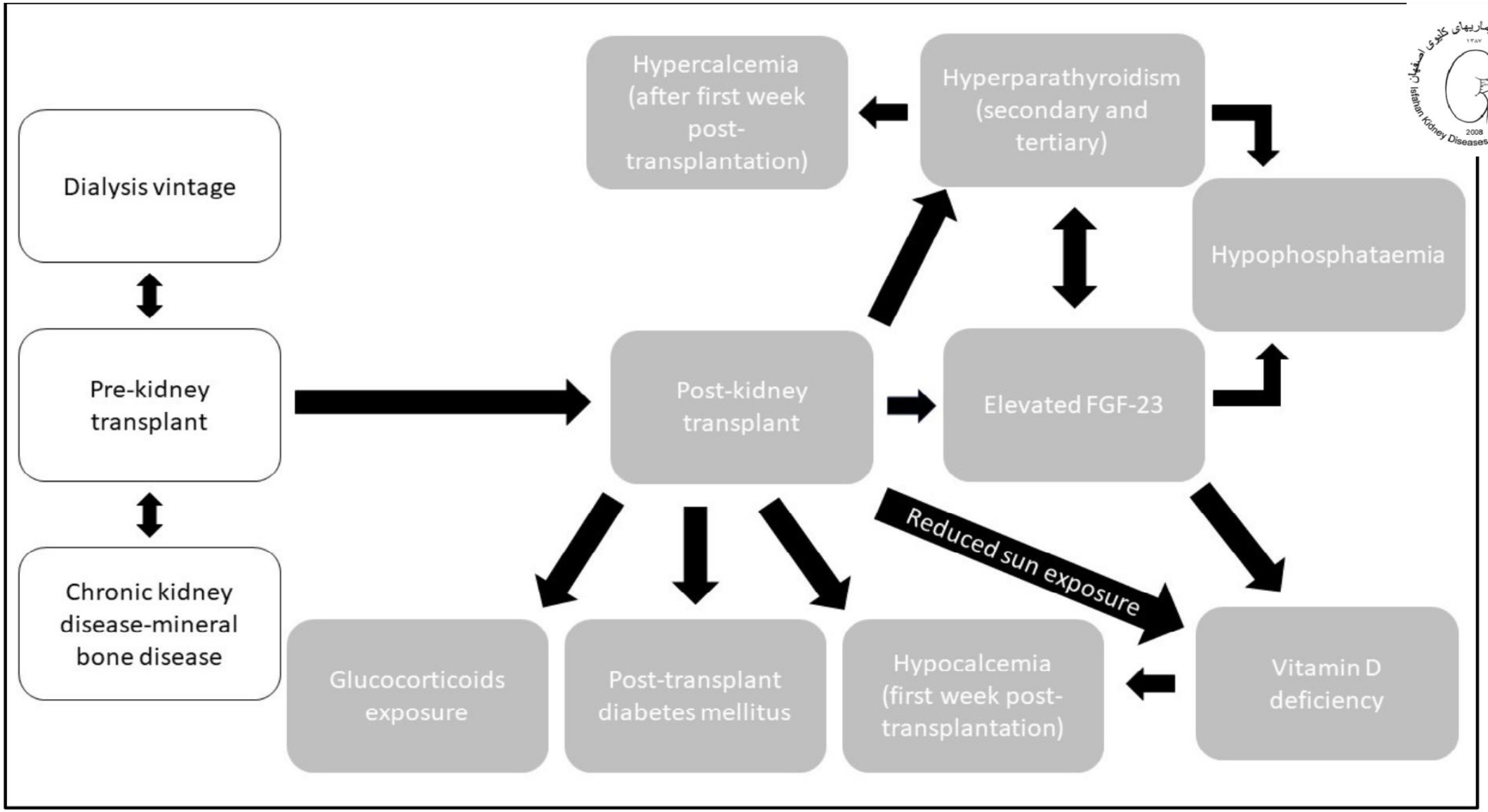

Figure 1. Main clinical and biochemical changes contributing to post-transplant bone disease: F
fibroblast growth factor-23.

Parathyroid Hormone

- Elevated parathyroid hormone (PTH) is associated with increased cortical bone loss.
- significant positive correlation between serum PTH before and after transplantation, therefore, **higher PTH level pre-transplantation carries a higher risk of persistent hyperparathyroidism following transplantation** .
- Persistent hyperparathyroidism portends an increased risk of developing PTBD , with a positive correlation with **fracture incidence**

Sizar, O.; Khare, S.; Goyal, A.; Givler, A. Vitamin D Deficiency. [Updated 2023 Jul 17]. In *StatPearls [Internet]*; StatPearls Publishing: Treasure Island, FL, USA, 2024. Available online: https://www.ncbi.nlm.nih.gov/books/NBK532266/ (accessed on 9 January 2024).

Calcium

- Serum calcium levels fluctuate after kidney transplantation.
- Calcium levels **decline significantly during the first week after transplantation** but increase significantly thereafter.
- A high pre-transplantation PTH level protects against hypocalcemia within the first week but subsequently increases the risk of hypercalcemia after the first week .
- Serum calcium levels significantly **rise from 1 week post-transplant to 4 weeks and remain elevated through to 12 months post-transplantation.**
- The secondary rise in serum calcium is attributed to an increase in 1,25-dihydroxycholecalciferol production in the functioning allograft post-transplantation and persistent hyperparathyroidism

Wolf, M.; Weir, M.R.; Kopyt, N.; Mannon, R.B.; Von Visger, J.; Deng, H.; Yue, S.; Vincenti, F. A Prospective Cohort Study of Mineral Metabolism After Kidney Transplantation. *Transplantation* **2016**, *100*, 184–193.

Hypercalcemia

- Importantly, hypercalcemia may be associated with the development of calcifications in the allograft that consequently affect graft survival

- Bone and Mineral Disease in Kidney Transplant Recipients /Pascale Khairallah1 and Thomas L. Nickolas2

CJASN 17: 121–130, 2022. doi: https://doi.org/10.2215/CJN.03410321 /kidney transplantation

Phosphate

- Serum phosphate **decreases in the early phase of transplantation from week 1 to week 4**, reflecting increased phosphaturia in the functioning allograft, which is stimulated by an elevated FGF-23 level.
- FGF-23 level decreases rapidly in the first 3 months post-transplantation and remains stable thereafter .
- Hypophosphataemia is observed in **90%** of patients in the early post-transplant period .
- Subsequently, serum phosphate gradually increases from **3 months through to 12** months post-transplantation.

Wolf, M.; Weir, M.R.; Kopyt, N.; Mannon, R.B.; Von Visger, J.; Deng, H.; Yue, S.; Vincenti, F. A Prospective Cohort Study of Mineral

Metabolism After Kidney Transplantation. *Transplantation* **2016**, *100*, 184–193.

Vitamin D

- 25-hydroxycholecalciferol deficiency is common after kidney transplantation.
- Multiple factors contribute to vitamin D deficiency after transplantation. These include:

- **decreased allograft function**

- **elevated FGF-23**

- **decreased PTH levels**

- Other contributing factors include reduced sun exposure, as patients are advised to adopt sun protection measures ,leading to reduced vitamin D absorption through the skin .

- Sizar, O.; Khare, S.; Goyal, A.; Givler, A. Vitamin D Deficiency. [Updated 2023 Jul 17]. In *StatPearls [Internet]*; StatPearls Publishing: Treasure Island, FL, USA, 2024. Available online: https://www.ncbi.nlm.nih.gov/books/NBK532266/ (accessed on 9 January 2024).

The Changing Epidemiology of Bone Strength after Transplantation

- Bone strength is defined as the combination of bone **density** and **quality.**
- Bone density refers to the amount of bone mineral (hydroxyapatite) per centimeter squared of bone tissue (i.e., gmHA/cm2), and in the clinic, it is measured by dual energy x-ray absorptiometry.
- Bone quality refers to bone tissue material properties (i.e., microarchitecture, turnover, mineral content and structure, collagen content) and is measured by tetracycline double-labeled bone biopsy with quantitative histomorphometry.

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The Changing Epidemiology of Bone Strength after Transplantation

- Historically, the **first 12–18 months of transplantation** were associated with **dramatic decreases in bone density of up to 9% at the spine and hip** .
- Over the long term, **BMD was reported to stabilize between the third and fifth years post-transplant**, increase by around 6% between the sixth and tenth years post-transplant, and increase by around 2% afterward

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Table 1. Classification of renal osteodystrophy.

Post-Transplant Bone Disease Including Renal Osteodystrophy [23]
Osteitis fibrosa/advanced hyperparathyroidism-related bone disease (high bone turnover)
Adynamic bone disease (low bone turnover)
Osteomalacia (low bone turnover)
Mixed renal osteodystrophy (either high or low bone turnover)
Osteopenia and osteoporosis *

* Not specific to kidney transplant recipients (KTRs).

Risk factors for osteoprosis after kidney transplant

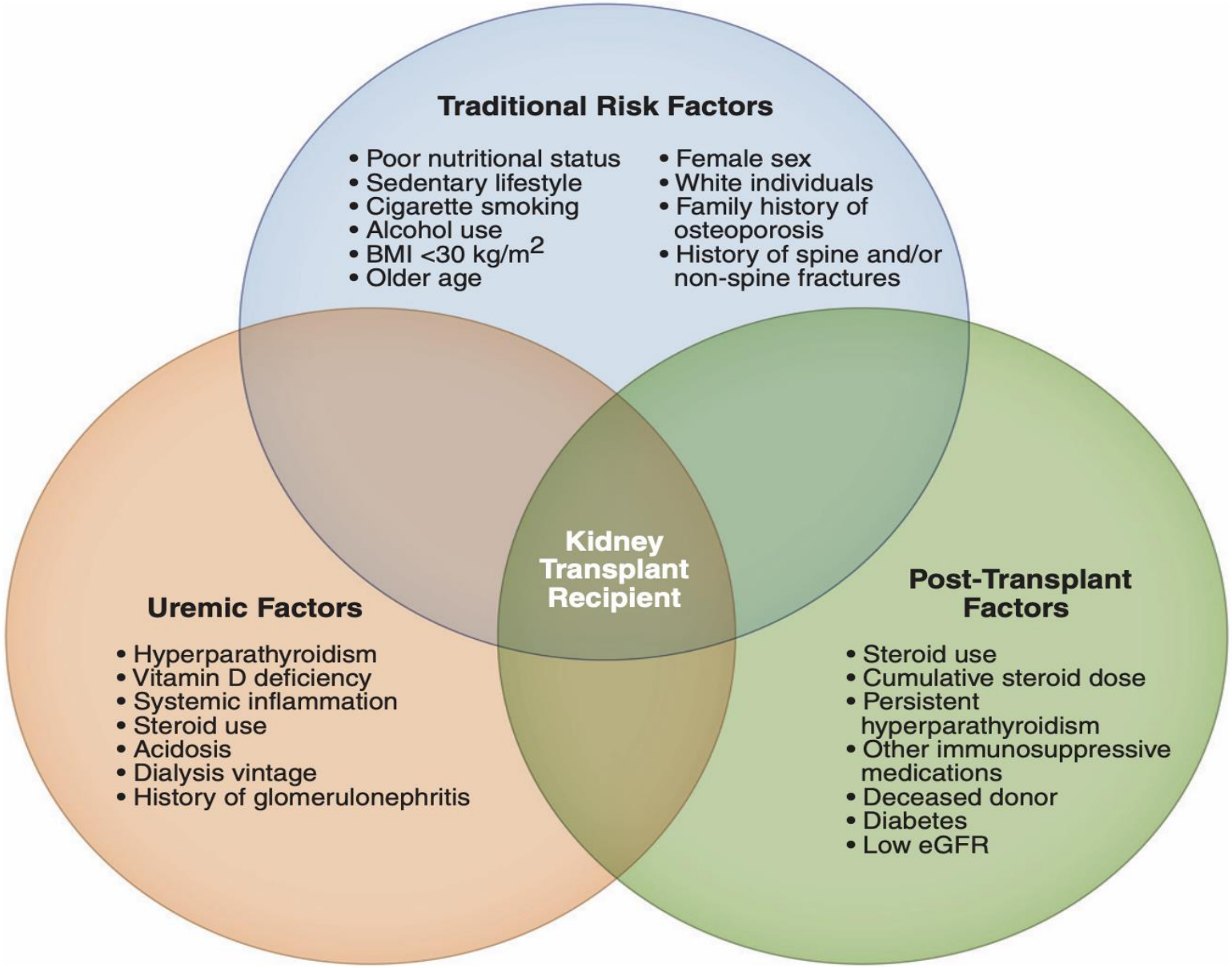

Figure 1. | **Pretransplant and post-transplant risk factors for osteoporosis.** BMI, body mass index.

Fragility Fractures

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- The risk factors for incident fragility fractures in patients living with a kidney transplant are:

- older age,

- female sex,

-concurrent diabetes,

-prior fracture,

-receipt of pre-transplantation dialysis,

- - glomerulonephritis and

-hypertension as the etiology of kidney failure,

- receipt of a kidney from a deceased donor,

-HLA-DR mismatch and

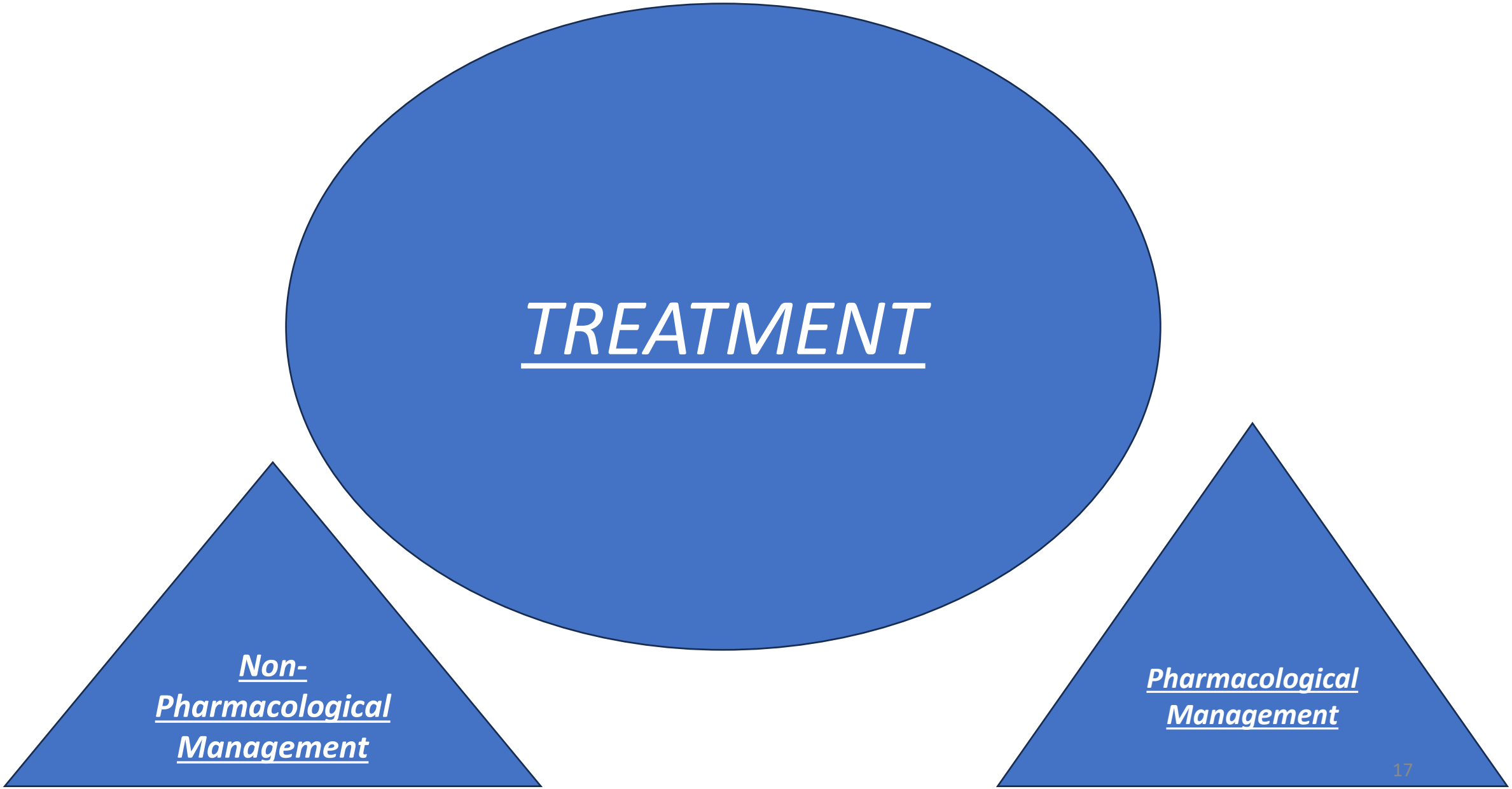
- elevated urine protein-to-creatinine ratio .

Batteux, B.; Nowak, A.; Séjourné, A.; Penet, C.; Masmoudi, K.; Brazier, F.; Laville, S.M.; Bennis, Y.; Gras-Champel, V.; Choukroun, G.; et al. Drugs associated with incident fragility fractures in kidney transplant recipients. *Clin. Kidney J.* **2023**, *16*, 571–584. [CrossRef]

Bone Turnover Markers

- PTH and bone-specific ALP (bALP) are mainly used as markers of bone turnover.
- A post hoc analysis of the POSTOP study in KTRs showed a negative correlation between bALP level and BMD at the hip and lumbar spine at 6 months follow-up .
- Consequently, bALP may be a better indicator of bone turnover.

Heimgartner, N.; Graf, N.; Frey, D.; Saleh, L.; Wüthrich, R.P.; Bonani, M. Predictive Power of Bone Turnover Biomarkers to Estimate Bone Mineral Density after Kidney Transplantation with or without Denosumab: A post hoc Analysis of the POSTOP Study. *Kidney Blood Press. Res.* **2020**, *45*, 758–767. [CrossRef]


TREATMENT
Non-Pharmacological Management
Pharmacological Management


Non-
Pharmacological
Management

Non-Pharmacological Management

- The National Osteoporosis Guideline Group strongly recommends :

- healthy, nutrient-rich balanced diet with an adequate intake of calcium (minimum 700 mg daily), preferably through diet or otherwise via supplementation,

- and to consume vitamin D from food or otherwise supplementation of at least 800 IU/day if they are vitamin D deficient or at risk of deficiency.

Haarhaus, M.; Aaltonen, L.; Cejka, D.; Cozzolino, M.; de Jong, R.T.; D'Haese, P.; Evenepoel, P.; Lafage-Proust, M.-H.; Mazzaferro, S.; McCloskey, E.; et al. Management of fracture risk in CKD—Traditional and novel approaches. *Clin. Kidney J.* **2023**, *16*, 456–472. [CrossRef] [PubMed]

Non-Pharmacological Management

- smoking cessation is recommended .
- Thus, tailored regular weight-bearing exercises and muscle-strengthening exercises should be encouraged among those at risk of osteoporosis to build muscle mass and strength and to improve balance.
- Introducing pragmatic measures to counter falls, including improving senses (hearing aids and glasses), adequate lighting when mobilizing and appropriate footwear to improve grip, are advi


Pharmacological
Management

Glucocorticoid Minimization

- Cumulative dose of corticosteroid negatively correlates with low trabecular bone volume and bone turnover but shows no effect on the mineralization status.

Haller, M.C.; Kammer, M.; Kainz, A.; Baer, H.J.; Heinze, G.; Oberbauer, R. Steroid withdrawal after renal transplantation: A retrospective cohort study. *BMC Med.* **2017**, *15*, 8. [CrossRef] [PubMed]

Calcium

- The recommended daily dietary allowance for calcium is between 1000 and 1200 mg based on age and sex .
- Elevated serum calcium has been associated with non-fatal cardiovascular events.
- Therefore, patients living with a kidney transplant should adhere to the recommended dietary allowance, ideally via dietary intake, if not, via supplementation, to maintain calcium levels within the normal range while avoiding hypercalcemia .
- The treatment of hypocalcemia can reduce the risk of secondary hyperparathyroidism and improve BMD in combination with vitamin D .

Ross, A.C.; Manson, J.E.; Abrams, S.A.; Aloia, J.F.; Brannon, P.M.; Clinton, S.K.; Durazo-Arvizu, R.A.; Gallagher, J.C.; Gallo, R.L.; Jones, G.; et al. The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What Clinicians Need to Know. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 53–58. [CrossRef]

Vitamin D

- The recommended daily dietary allowance for vitamin D is between 600 and 800 IU, depending on age and sex .
- Vitamin D deficiency is common post-transplantation.
- Vitamin D treatment reduces the rate of persistent hyperparathyroidism at 1 year post-transplantation from 39% to 25% .

- Given this new evidence, treatment with cholecalciferol after kidney transplantation should be especially targeted in those with:

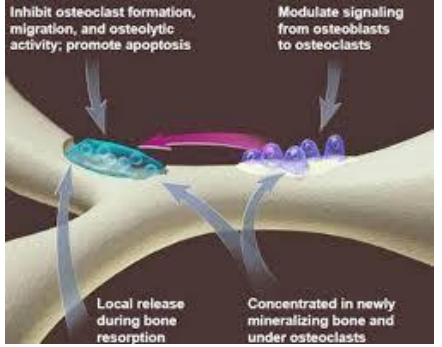
- osteopenia or osteoporosis on BMD,

-vitamin D deficiency and/or

-elevated PTH level.

Tsujita, M.; Doi, Y.; Obi, Y.; Hamano, T.; Tomosugi, T.; Futamura, K.; Okada, M.; Hiramitsu, T.; Goto, N.; Isaka, Y.; et al. Chole ss in I Endpoint Analysis of a Randomized Controlled Trial. *J. Bone Miner. Res.* **2022**, *37*, 303–311. [CrossRef]

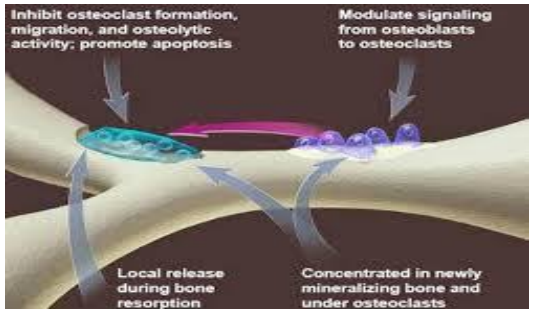
Bisphosphonates



- Bisphosphonates are analogues of inorganic pyrophosphate.
- They bind to hydroxyapatite crystals with high affinity for bone minerals.
- They inhibit hydroxyapatite breakdown, thus suppressing bone resorption .
- A systematic review by Palmer et al. showed that bisphosphonate therapy in a kidney transplantation cohort significantly **improved BMD by DXA at the lumbar spine and femoral neck** when compared to placebo or no treatment, but there was no difference in fracture rates .

Drake, M.T.; Clarke, B.L.; Khosla, S. Bisphosphonates: Mechanism of Action and Role in Clinical Practice. *Mayo Clin. Proc.* **2008**, *83*, 1032–1045. [CrossRef] [PubMed]

Bisphosphonates …



- Bisphosphonates can cause adverse events such as osteonecrosis of the jaw, atypical femoral fracture and severe hypocalcemia .
- Therefore, bisphosphonate use should be considered in those with a high risk of fracture but should be used with caution, especially in those who may have adynamic bone disease.

Hauck, D.; Nery, L.; O'Connell, R.; Clifton-Bligh, R.; Mather, A.; Girgis, C.M. Bisphosphonates and bone mineral density in patients with end-stage kidney disease and renal transplants: A 15-year single-centre experience. *Bone Rep.* **2022**, *16*, 101178.

Denosumab

- Denosumab is a fully human IgG2 monoclonal antibody that binds human receptor activator of NF-κB ligand (RANKL) with high affinity.
- Its use reduces osteoclast numbers and bone turnover, resulting in a significant increase in bone mass and density at the spine and hip.
- The use of denosumab in KTRs may be associated with **significantly higher rates of urinary tract infections and diarrhea compared to placebo .**

Lacey, D.L.; Boyle, W.J.; Simonet, W.S.; Kostenuik, P.J.; Dougall, W.C.; Sullivan, J.K.; Martin, J.S.; Dansey, R. Bench to bedside: Elucidation of the OPG–RANK–RANKL pathway and the development of denosumab. *Nat. Rev. Drug Discov.* **2012**, *11*,401–419. [CrossRef] [PubMed]

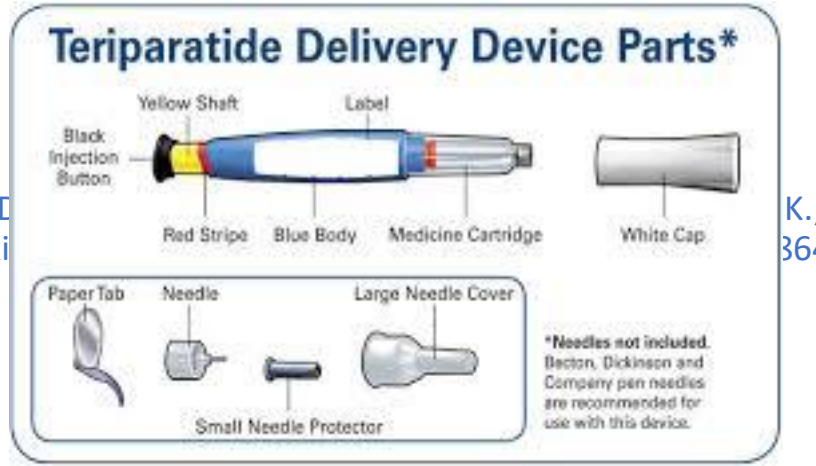
Denosumab

- Hypocalcemia tends to occur in those with more advanced renal impairment (CKD IV–V) in the first week after denosumab treatment .
- Hence, **calcium and vitamin D levels should be monitored before and within 1 month of treatment** with denosumab to prevent and allow for prompt treatment of hypocalcemia.
- Hypocalcemia, when detected, should be treated with increased calcium supplementation .

- Alfieri, C.; Binda, V.; Malvica, S.; Cresseri, D.; Campise, M.; Gandolfo, M.T.; Regalia, A.; Mattinzoli, D.; Armelloni, S.; Favi, E.; et al. Bone Effect and Safety of One-Year Denosumab Therapy in a Cohort of Renal Transplanted Patients: An Observational Monocentric Study. *J. Clin. Med.* **2021**, *10*, 1989.

Teriparatide

- Teriparatide is a medication used in the management and treatment of osteoporosis.
- The drug is in the **anabolic class of osteoporosis medications**.
- Human parathyroid hormone is a powerful osteoanabolic agent made up of the first 34 amino acids of the N-terminal.
- A double-blind randomised controlled trial with a 6-month follow-up completed in 24 KTRs by Cejka et al. showed that femoral BMD remained stable with 20 mcg/day teriparatide.



Cejka, D … K.; Pietschmann, P … After Ki… 364–1870.

Who should not take teriparatide?

- Bone cancer, or history of or. High levels of alkaline phosphatase (enzyme found in the bones) or.
- Metabolic bone disease (eg, Paget's disease of the bone) or.
- Open epiphyses (bones are still growing)
- hypercalcemia

Calcimimetics

- Cinacalcet **has not been approved** for use in patients living with a kidney transplant for the treatment of hyperparathyroidism .
- However, studies have shown the safe and efficacious use of cinacalcet for treating hyperalcemia in secondary hyperparathyroidism, resulting in a significant reduction in serum calcium and a rise in serum phosphate among KTRs .

Evenepoel, P.; Cooper, K.; Holdaas, H.; Messa, P.; Mourad, G.; Olgaard, K.; Rutkowski, B.; Schaefer, H.; Deng, H.; Torregrosa, J.V.; et al. A randomized study evaluating cinacalcet to treat hypercalcemia in renal transplant recipients with persistent hyperparathyroidism. *Am. J. Transplant.* **2014**, *14*, 2545–2555.

Parathyroidectomy

-Persistent hypercalcemia,

-Nephrocalcinosis/ nephrolithiasis,

- High bone turnover states resistant to medical therapies .

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CONCLUSION

Conclusions

PTBD includes, the development of

- hypocalcemia,
- hypercalcemia,
- hypomagnesaemia,
- hypophosphataemia,
- vitamin D deficiency,
- hyperparathyroidism,
- Osteomalacia , osteopenia and osteoporosis.

Conclusions

- The gold standard to diagnose PTBD is to perform a bone biopsy.
- However, bone biopsy is not readily available, is time-consuming and has associated risks.
- There is a growing body of evidence to support the use of **other biomarkers** as surrogates.
- There are multiple tools available that can be used to help decision making in terms of diagnosis and management.
- These include the **FRAX score for fracture risk**, an assessment of **BMD** using DXA and bone turnover markers.
- Ideally, optimal calcium and vitamin D intake should be achieved with dietary measures in the first instance.

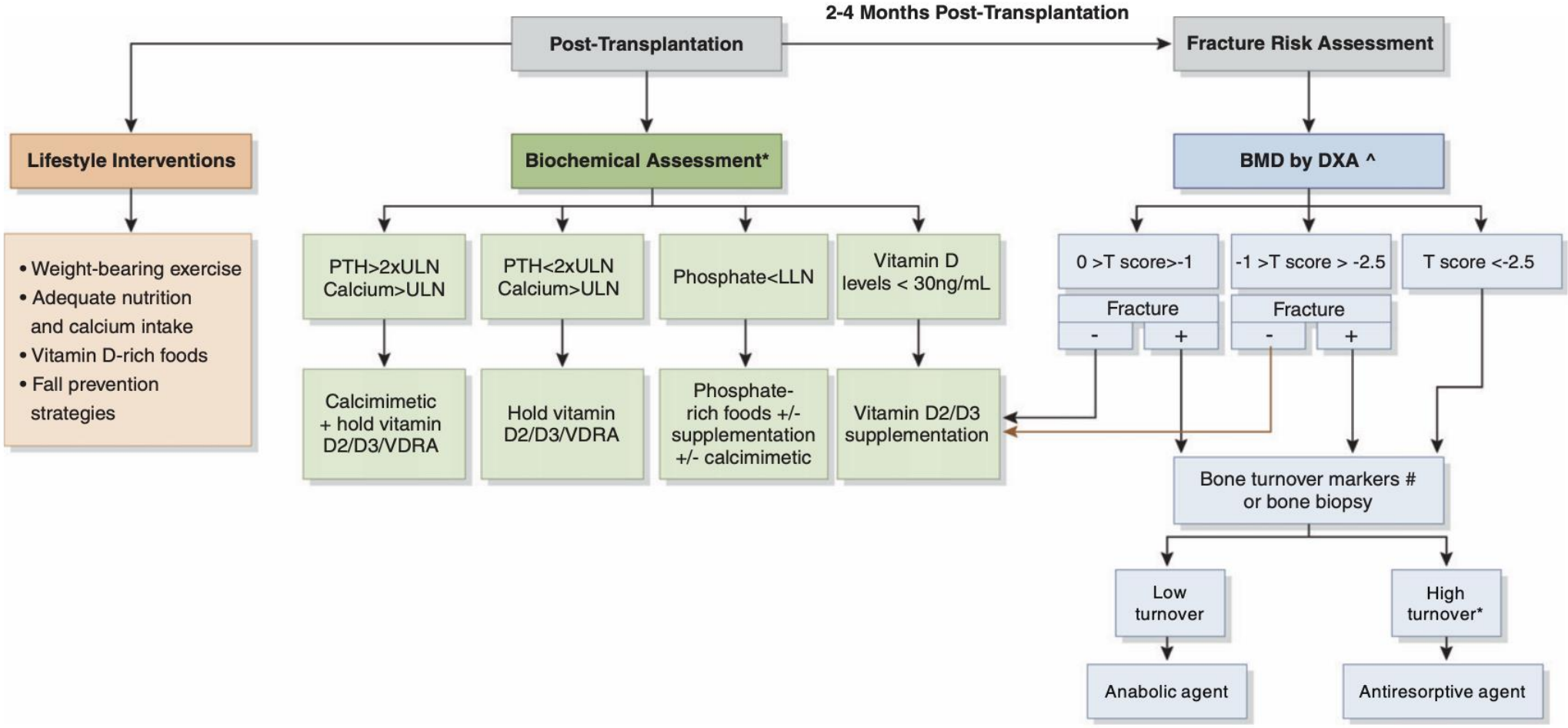

Figure 2. | **Risk-based approach to mineral and bone disease (MBD) management after kidney transplantation.** *Parathyroidectomy should

International Journal of
Molecular Sciences

MDPI

Review

Post-Transplant Bone Disease in Kidney Transplant Recipients: Diagnosis and Management

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* Correspondence: david.lappin@hse.ie

Abstract: Kidney transplantation is the preferred gold standard modality of treatment for kidney failure. Bone disease after kidney transplantation is highly prevalent in patients living with a kidney transplant and is associated with high rates of hip fractures. Fractures are associated with increased healthcare costs, morbidity and mortality. Post-transplant bone disease (PTBD) includes renal osteodystrophy, osteoporosis, osteonecrosis and bone fractures. PTBD is complex as it en-

Bone and Mineral Disease in Kidney Transplant Recipients

Pascale Khairallah[1] *and Thomas L. Nickolas*[2]

Abstract

After kidney transplantation, mineral and bone disorders are associated with higher risk of fractures and consequent morbidity and mortality. Disorders of calcium and phosphorus, vitamin D deficiency, and hyperparathyroidism are also common. The epidemiology of bone disease has evolved over the past several decades due to changes in immunosuppressive regimens, mainly glucocorticoid minimization or avoidance. The assessment of bone disease in kidney transplant recipients relies on risk factor recognition and bone mineral density assessment. Several drugs have been trialed for the treatment of post-transplant mineral and bone disorders. This review will focus on the epidemiology, effect, and treatment of metabolic and skeletal derangements in the transplant recipient.

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Introduction

After kidney transplantation, disorders of mineral and bone metabolism are common and are important causes of morbidity and mortality (1–4). Post-transplantation mineral and bone disease (MBD) is defined by clinical features that are similar to, but distinct from, MBD

Importantly, hypercalcemia may be associated with the development of calcifications in the allograft that consequently affect graft survival (18).

Hypophosphatemia develops in up to 90% of post-transplant recipients (6,8). It typically develops in the first 3 months post-transplant and improves in approx-

IJKD TRANSPLANTATION

Low-dose Pamidronate for Treatment of Early Bone Loss Following Kidney Transplantation

A Randomized Controlled Trial

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Keywords. pamidronate, bone mineral density, kidney transplantation, calcium, hydroxyvitamin D

Original Paper

Introduction. Kidney transplantation is associated with rapid loss of bone mineral density (BMD) in the first months after transplantation. The effect of pamidronate on bone loss after transplantation was evaluated in a randomized controlled trial.

Materials and Methods. Forty patients were enrolled in this study (16 in the pamidronate group and 24 in the control group). Pamidrinate was administered as 30-mg intravenous infusion within 2 days after transplantation and 3 months later. All of the patients received calcium and vitamin D supplementation. Laboratory parameters and BMD (lumbar spine and femoral neck) were measured at baseline and 6 months after kidney transplantation.

Results. Bone mineral density at the initiation of study had no significant differences between the two groups. In each group, BMD of femoral neck and lumbar spine had no significant differences 6 months after transplantation in comparison to pretransplantation values. There was no significant difference in BMD changes after intervention between two groups. Parathyroid hormone level normalized in both of the pamidronate and control groups 6 months after kidney transplantation. Glomerular filtration rate at the end of study was not significantly different between the two groups.

Conclusions. Our study suggests that administration of calcium and vitamin D following transplantation may be beneficial to counterbalance the substantial bone loss occurring within 6 months after transplantation, and addition of pamidronate has no beneficial effect in BMD in this short interval after kidney transplantation.

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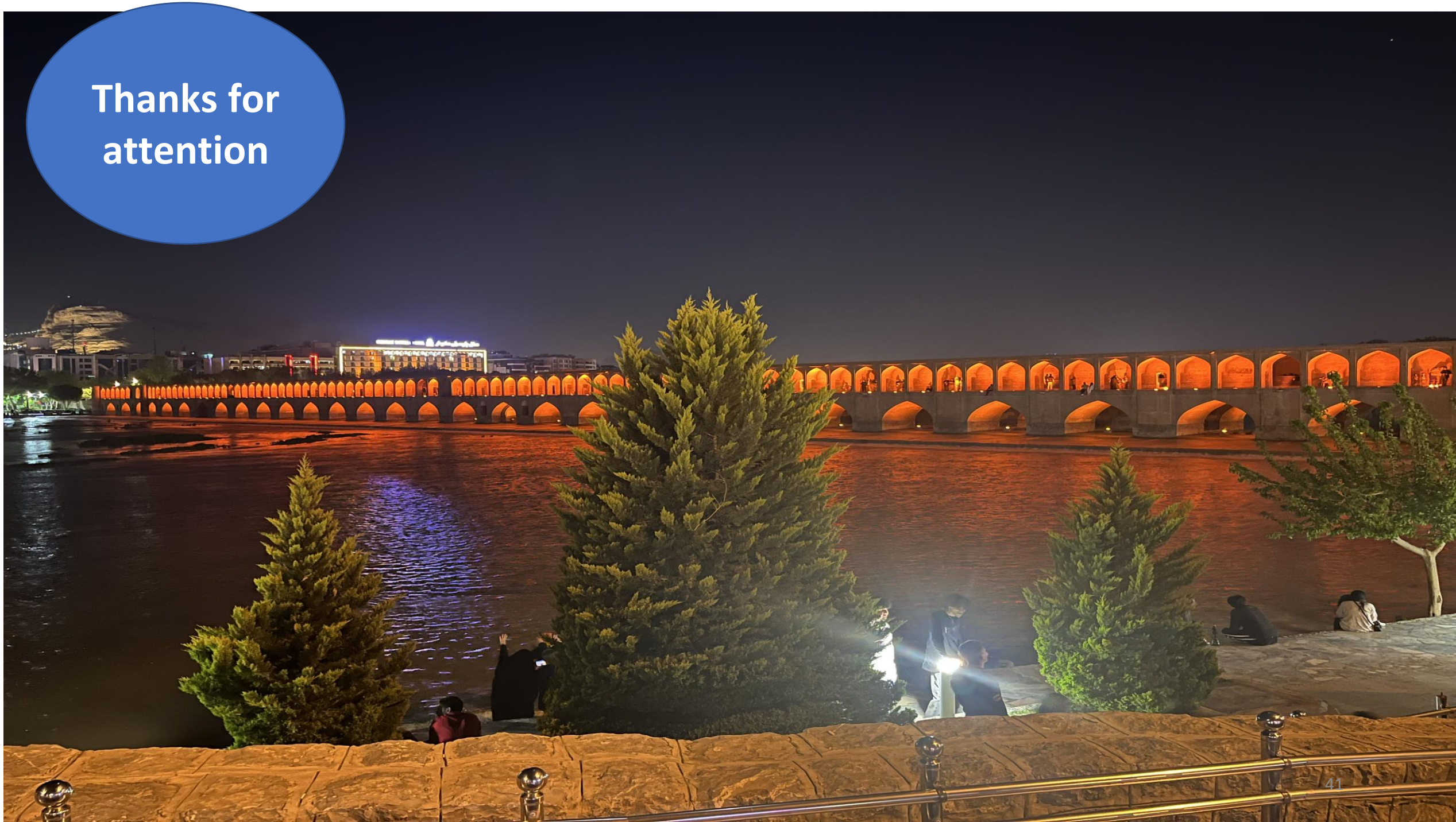
Thanks for attention