Mineral and Bone disorders in Kidney Transplant recipients

Bone Disease after Kidney Transplantation

Introduction:

- Bone disease post-transplantation is a major cause of morbidity in kidney transplant recipients, with a significantly higher risk of fractures hospitalization, and mortality.

- Post–transplantation bone disease is characterized by changes in bone quality and density as well as mineral metabolism.

Bone Disease after Kidney Transplantation

Epidemiology:

- The spectrum of bone diseases in kidney transplant recipients includes renal osteodystrophy, osteoporosis, bone fracture, and osteonecrosis.
- BMD declines by :
  - ✓ 4%–10% in the first 6 months.
  - ✓ 0.4%–4.5% in lumbar BMD between 6 and 12 months.
  - ✓ After 1 year, BMD remains relatively stable with no further decline.

Bone Disease after Kidney Transplantation

- This reduction in BMD contributes to an increased risk of fractures. In the first 5 years after transplantation.

- The most common fracture locations are the hip and ankle/foot, with hip fracture usually associated with osteoporosis.

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Table 1. Risks factors associated with post-transplantation bone loss and fractures

Risk factors for osteoporosis

- General factors
  - *Younger age at transplantation*
  - *Poor nutrition*
  - *Smoking*
  - *Alcohol abuse*
- Endocrine/mineral factors
  - *Hypogonadal status*
  - *Hypomagnesemia*
- Biologic abnormalities
  - *Functionally different alleles of the vitamin D receptor gene*

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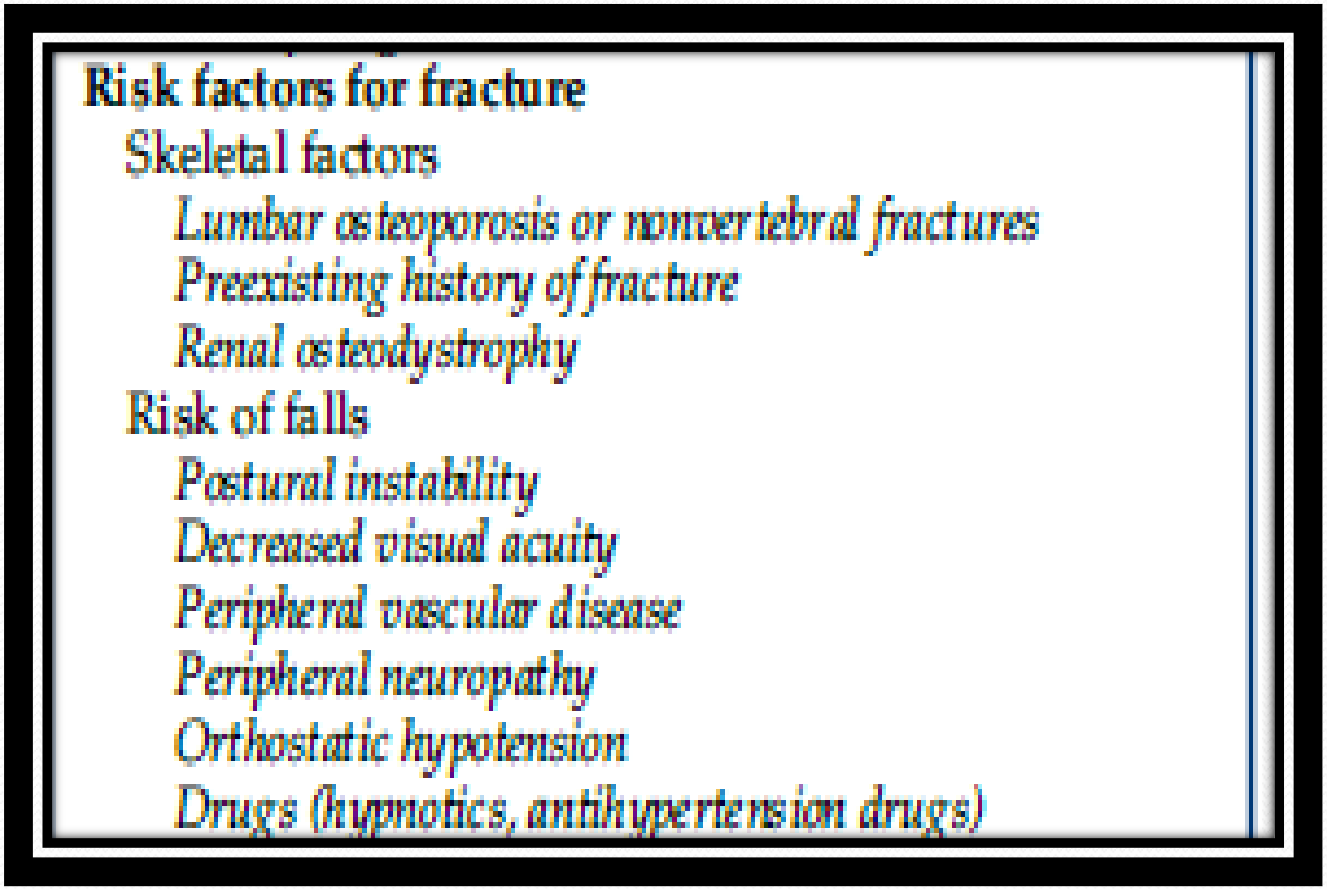

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Risk factors for both fracture and osteoporosis

- General factors
  - *Age ≥50 yr old*
  - *Women*
  - *Body mass index <23 kg/m²*
  - *Diabetes*
  - *Time on dialysis*
- Transplantation factors
  - *Cumulative dose of corticosteroids*
- Biologic abnormalities
  - *Vitamin D deficiency*
  - *Parathyroid hormone >130 ng/L*
  - *High serum fibroblast growth factor 23 level*

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- The rate of fracture has decreased in recent years. This trend partly reflects :
  - ✓ a significant reduction in cumulative glucocorticoid (GC) exposure.
  - ✓ improved management of CKD-MBD.
  - ✓ pretransplantation bone protection strategies, such as vitamin D and bisphosphonates in kidney transplant recipients, as well as changes in lifestyle and physical activity.

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Pathophysiology of Post–Transplant Bone Disease:

- 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 .
- In contrast, before transplantation, bone loss preferentially affects the cortical bone mainly because of secondary hyperparathyroidism (SHPT).

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- 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
  - ✓ disturbances in mineral metabolism, including an increased level of fibroblast growth factor 23, ongoing SHPT, and vitamin D deficiency.

Bone Disease after Kidney Transplantation

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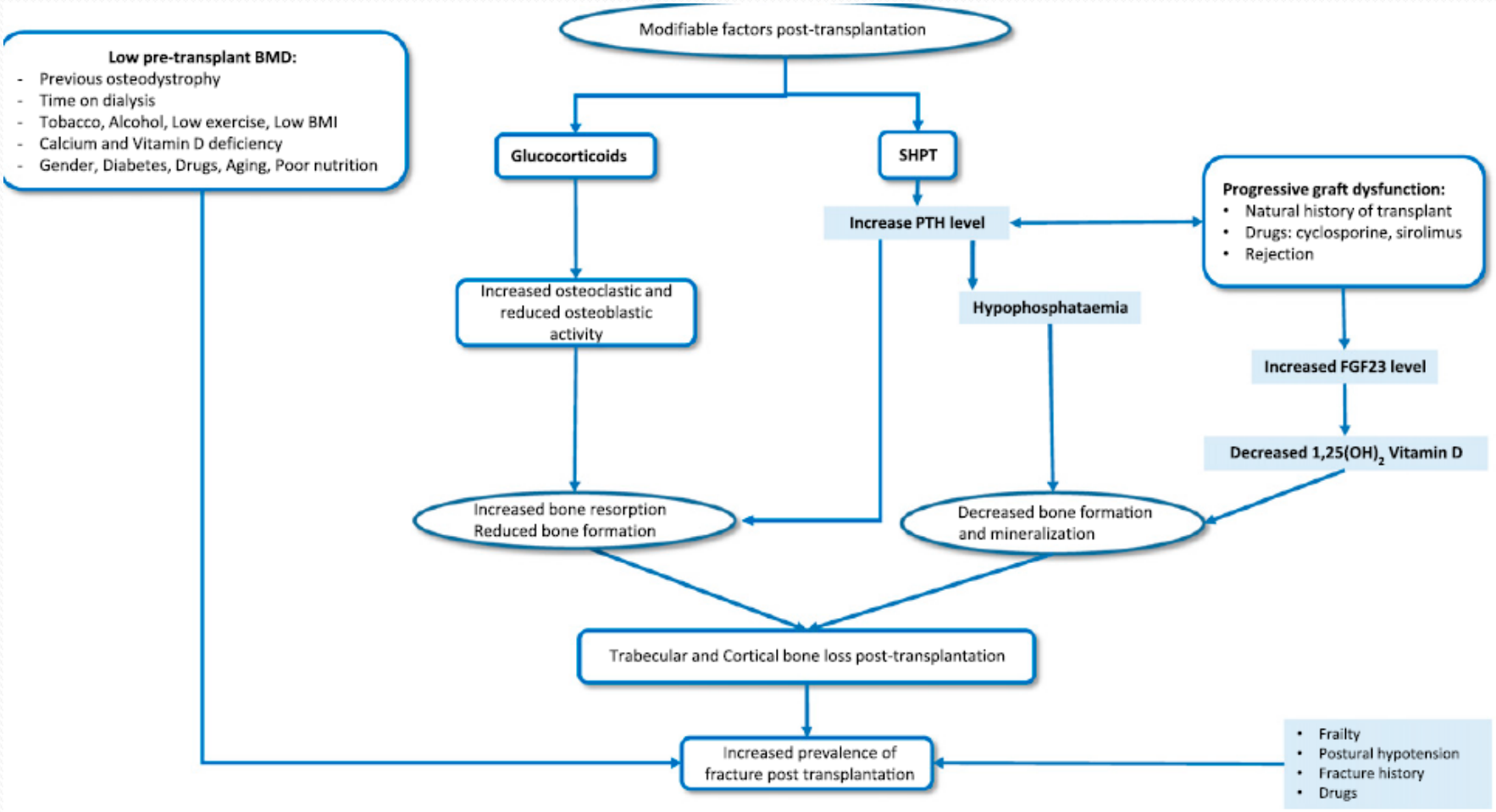
- **Progressive loss of kidney function after transplantation** increases the risk of worsening or de novo development of hyperparathyroidism with active vitamin D deficiency that leads to changes in bonehistomorphometry similar to those observed before transplantation.

Pathophysiology of bone loss and fractures before and after transplantation



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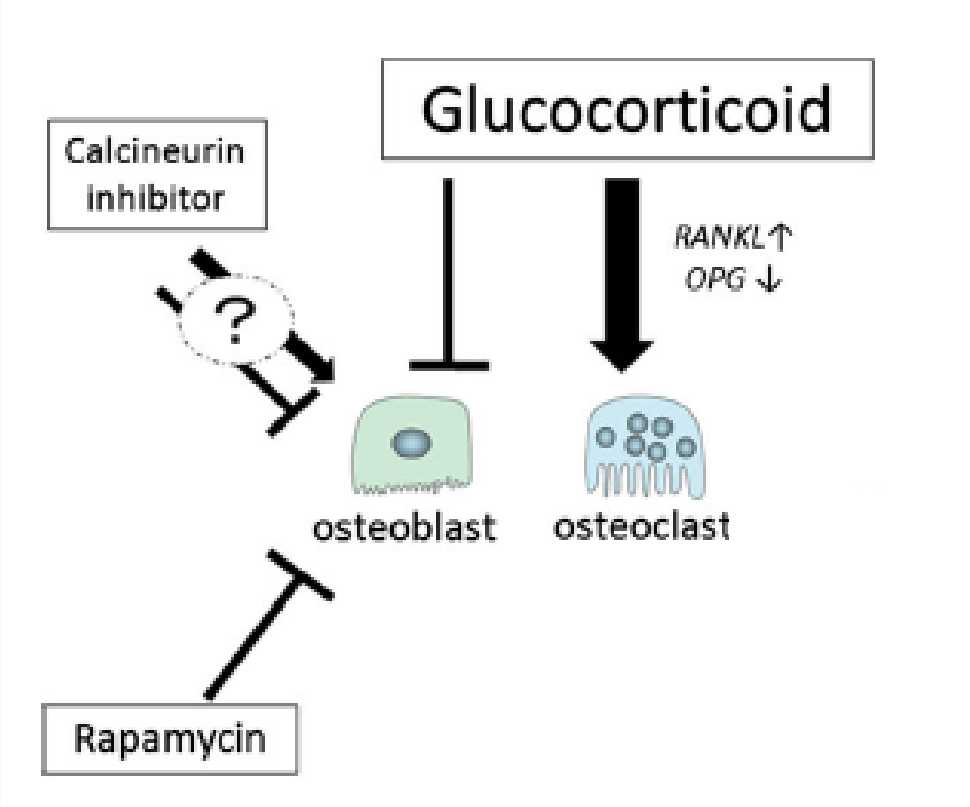
Immunosuppressants on bone metabolism



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Immunosuppressants on bone metabolism

Immunosuppressant	Effects	Mechanisms
Glucocorticoid	Formation	Osteoblast number and activity ↓
		Bone formation mediators ↓
		(Testosterone, TGFβ, IGF etc.)
		Bone matrix protein production ↓
	Resorption	Osteoclast activity ↑
		RANKL expression↑
		Osteoprotegerin ↓
		PTH production ↑, Ca/P ↓, active vitamin D ↓
Cyclosporine A	Formation	Osteoblast number ↓
		Osteoblast differentiation ↑
	Resorption	Osteocalcin ↑
Tacrolimus	Formation	Osteoblast differentiation ↑
		Osteoblast ERK1/2 signal ↓
	Resorption	Osteoclast number ↓
		Osteoclast differentiation ↑
Mycophenolate mofetil		unknown
Rapamycin	Formation	Osteoblast differentiation ↓
Sirolimus	Resorption	Osteoclast apoptosis ↑

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continue…

- For transplant recipients who already had a markedly reduced bone density before transplantation, immunosuppression therapy with a prednisolone dose\5 mg or no steroids (“steroidfree”) may also be considered .

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Evaluating Fracture Risk:

- *Role of DXA in Fracture Risk*

  A DXA scan is a relatively accurate, noninvasive, cost–effective screening method for estimating bone mass, and it seems to help predict fracture risk in kidney transplant recipients.

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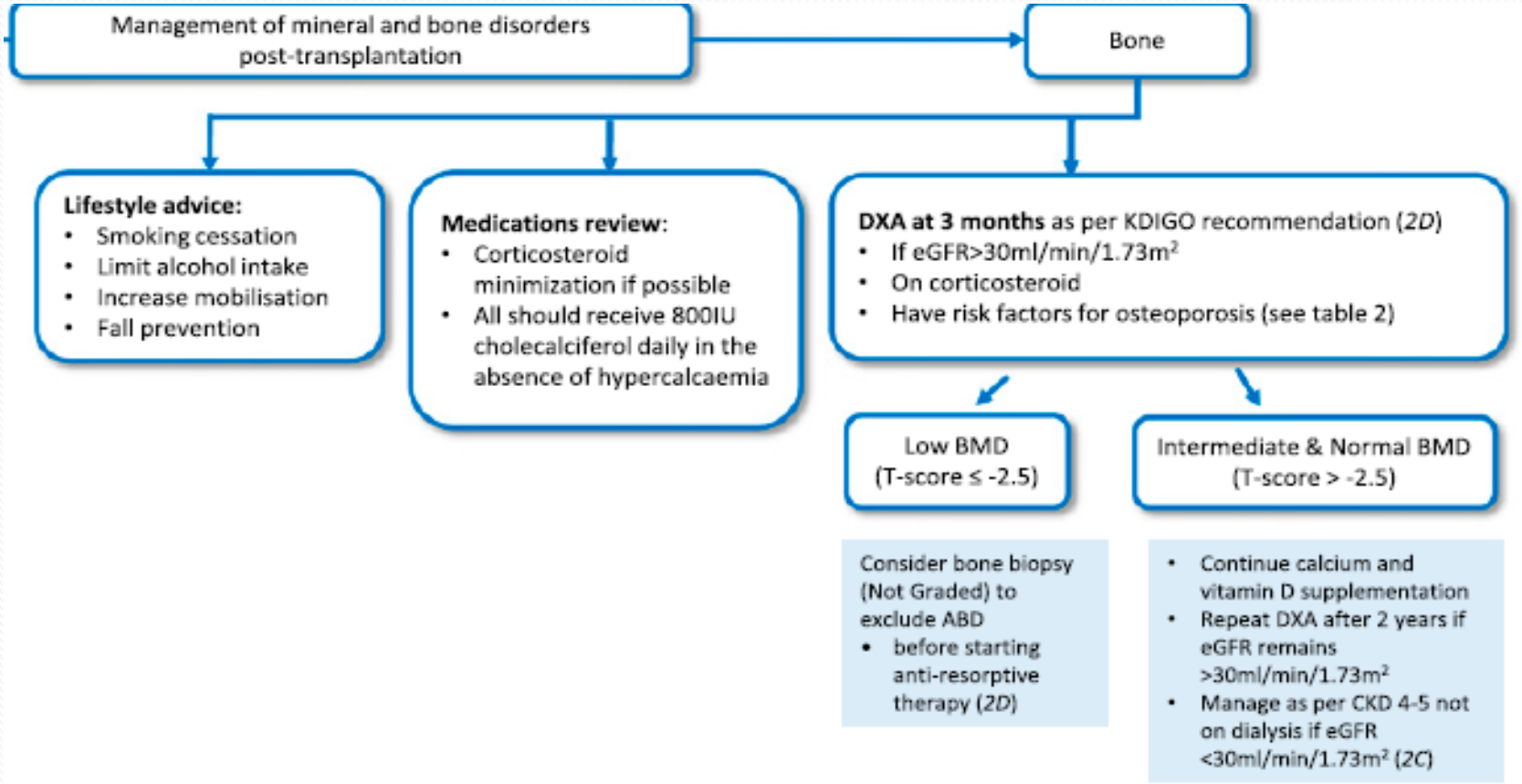
Bone Biopsy:

- Bone biopsy with double-tetracycline labeling is the gold standard to accurately diagnose post–transplantation bone disease subtype, but it is not often performed.

- KDIGO CKD-MBD guideline states that it is reasonable to consider bone biopsy to guide treatment in the first 12 months post-transplant.

Bone Disease after Kidney Transplantation

Preventing and Managing Bone Disease Post-Transplantation



Bone Disease after Kidney Transplantation

Preventing and Managing Bone Disease Post-Transplantation:

- *Recombinant PTH*

Recombinant PTH (teriparatide) is an anabolic agent, which can improve BMD in patients with GC-induced and postmenopausal osteoporosis.

Bone Disease after Kidney Transplantation

Continuo…

- **Antiresorptive Agents:**

- *Bisphosphonates* commonly used antiresorptive agents for osteoporosis.
- *Bisphosphonates* can potentially induce low bone turnover, and therefore, it is important to consider a bone biopsy before initiating therapy in those at high risk of ABD.
- treatment is well tolerated in kidney transplant recipients with a GFR.30 ml/min per 1.73 m2

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Continuo…

- **Antiresorptive Agents:**
  - *Denosumab*, a humanized monoclonal antibody against the receptor activator of NF-kB ligand, decreases bone resorption, significantly increases BMD, and decreases the risk of vertebral, nonvertebral, and hip fractures in osteoporosis.

Bone Disease after Kidney Transplantation

- **Vitamin D and Vitamin D Analogs:**
  - Supplementation with both active [1,25(OH)2D] and native (25-OHD) vitamin D can reduce loss of BMD

NEPHROLOGY

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Management of mineral and bone disorders in renal transplant recipients

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- The management of post-transplantation bone disease is a complex problem that remains under-appreciated in clinical practice.

- The treatment of post-transplantation bone loss should begin pre-transplantation. All patients active on transplant waiting lists should be screened for bone disease.

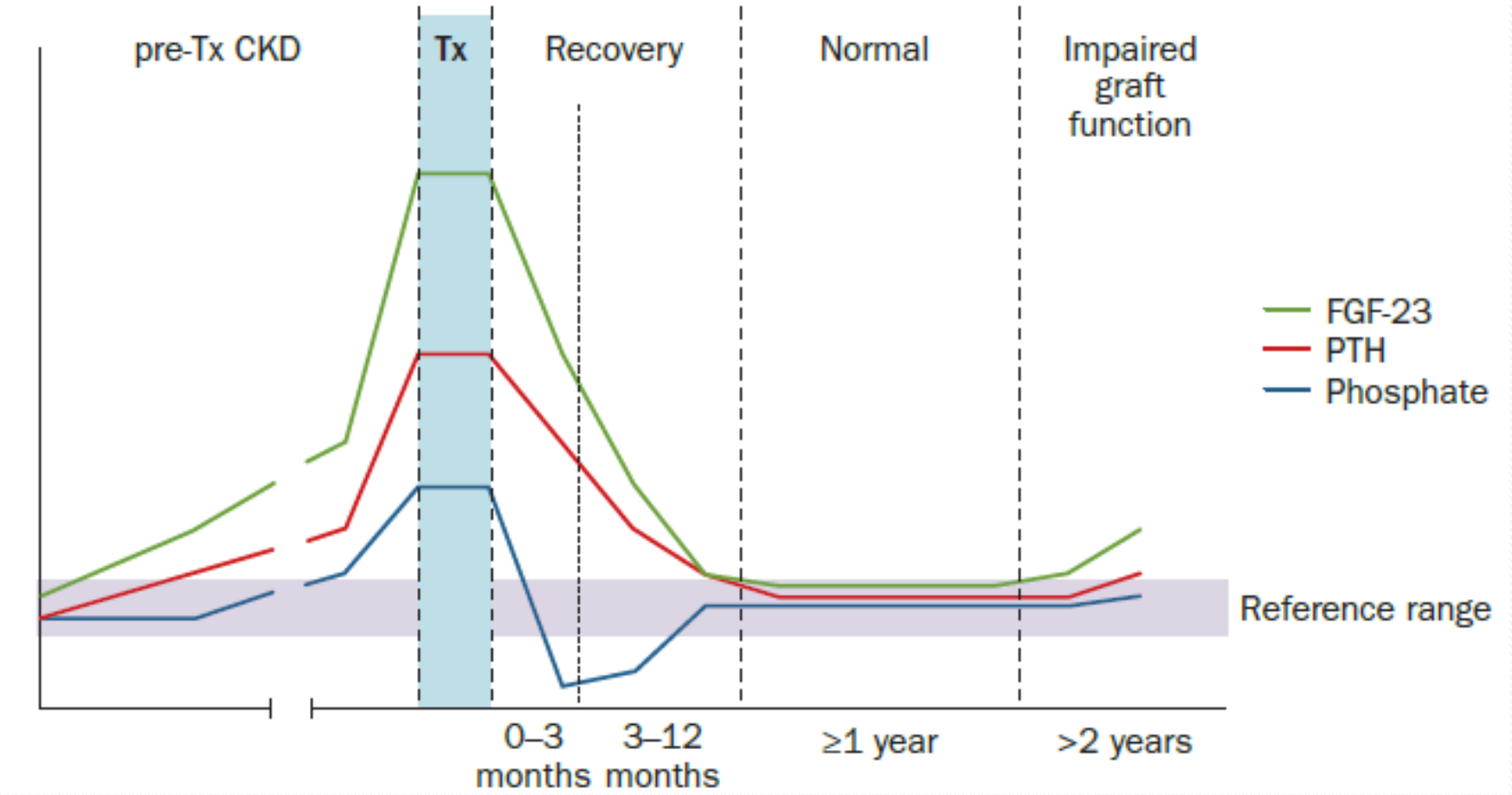
Mineral Disorder in Kidney Transplantation recipients

Screening and diagnosis

Biochemical assessment:

- KDIGO guidelines recommend the measurement and calcium and phosphate at least weekly until levels normalize.
- PTH and serum25(OH)D levels are also commonlymeasured; however, there is no recommendation or agreement as to the threshold level for intervention, or what constitutes an acceptable level.

Mineral Disorder in Kidney Transplantation recipients



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29 September 2015.

Phosphate and FGF-23 homeostasis after kidney transplantation

Box 1 | Abnormalities in phosphate homeostasis

First year after transplantation

- Post-transplantation hypophosphataemia (weeks to months)
- High, but declining levels of FGF-23 and PTH (months)

Stable transplant recipient with good graft function

- Low–normal serum phosphate
- FGF-23 usually in the normal range
- Persistent secondary or tertiary hyperparathyroidism may be present

Impaired renal function, development of graft failure

- Increased levels of FGF-23
- Secondary or tertiary hyperparathyroidism
- Hyperphosphataemia

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Phosphate homeostasis after kidney transplantation:

- Abnormalities in phosphate homeostasis are common in renal transplant recipients, ranging from hypophosphataemia within 3 months after transplantation to hyperphosphataemia.

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Mineral Disorder in Kidney Transplantation recipients

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- Persistent high levels of FGF-23 and parathyroid hormone during the first months post-transplantation.
- the influence of immunosuppressive drugs.
- ischaemia.reperfusion injury.
- metabolic acidosis.

can result in post-transplantation hypophosphataemia

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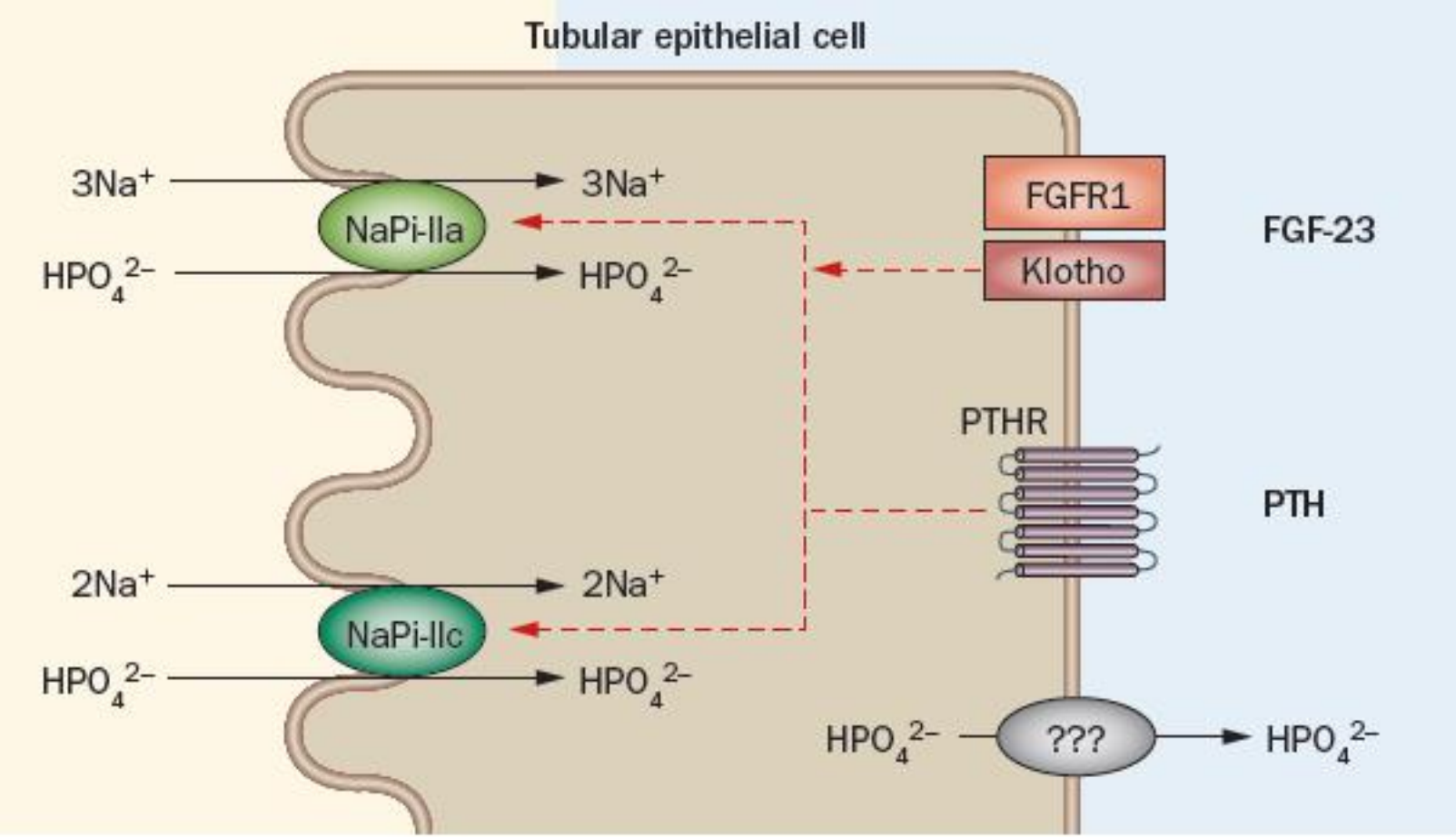
Phosphate homeostasis after kidney transplantation



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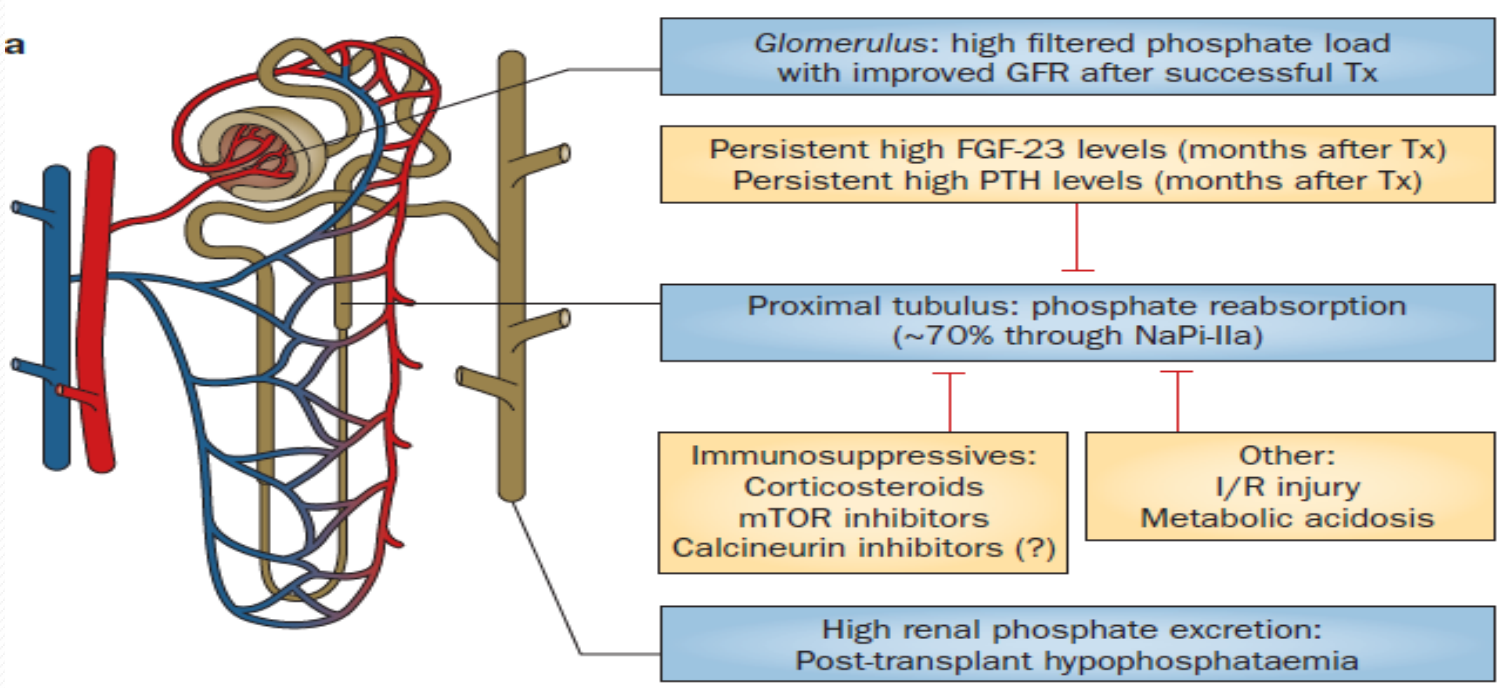
Mineral Disorder in Kidney Transplantation recipients

Development of hypophosphataemia after kidney transplantation



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Mineral Disorder in Kidney Transplantation recipients

Impact on the kidney:

- A high level of serum phosphate calcium–phosphate product or FGF-23 have all been independently associated with an increased risk of graft failure after kidney transplantation.

- In kidney transplantation, a higher FGF-23 level has been associated with worse renal function and a higher risk of rejection.

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Impact on bone:

- Post-transplantation hypophosphataemia can have a detrimental effect on bone mineralization and early osteoblast apoptosis, which further contributes to post-transplantation osteoporosis

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Mineral Disorder in Kidney Transplantation recipients

Mineral monitoring:

- The KDIGO guidelines recommend that serum calcium and phosphate levels are measured at least weekly until stable.

- Once mineral metabolism has stabilized, the monitoring intervals may be prolonged, varying from every 6–12 months

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Mineral Disorder in Kidney Transplantation recipients

Phosphate supplementation:

- We generally use a serum phosphate level of 0.5 mmol/l as a lower cut-off to consider initiating supplementation therapy in patients at our centres, as clinical symptoms (mainly muscle weakness) can develop at levels below this value.
- Supplementation can be accompanied by adverse gastrointestinal effects, but more importantly, can also exacerbate an already existing secondary hyperparathyroidism and further elevate FGF-23 levels.

Mineral Disorder in Kidney Transplantation recipients

Restoring phosphate homeostasis

I. Dietary interventions

II. Pharmacologic interventions:

- the renal transplant population, phosphate binders have to be used with caution given their effect on the availability of the immunosuppressant drug, (MMF), as phosphate binders have been shown to reduce the peak concentration and area under the curve of this agent

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Management of Post.transplant Hyperparathyroidism

- One of the accompanying conditions from CKD that can remain problematic post- transplantation is secondary hyperparathyroidism (SHPT).

- post-kidney transplantation showing an initial decrease in the PTH levels within the first 12 months post-transplant. However, in up to 50% of patients there is evidence of a persistent elevation in the PTH years after a successful transplantation

Division of Nephrology, Washington University in StDrugs (2019) 79:501–513

Management of Post.transplant Hyperparathyroidism

- Most transplant physicians will allow up to 12 months posttransplant for normalization of PTH.

- Past this point, a PTH level greater than two times normal (> 130 pg/mL) is consistent with persistent post-transplant hyperparathyroidism (PT-HPT).

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Management of Post.transplant Hyperparathyroidism

Pathophysiology:

- One of the main drivers of persistent SHPT is the enlarged PT glands due to hyperplasia that can occur during longstanding SHPT.

- the parathyroid tissue first undergoes diffuse hyperplasia, and in some patients develops into nodular hyperplasia.

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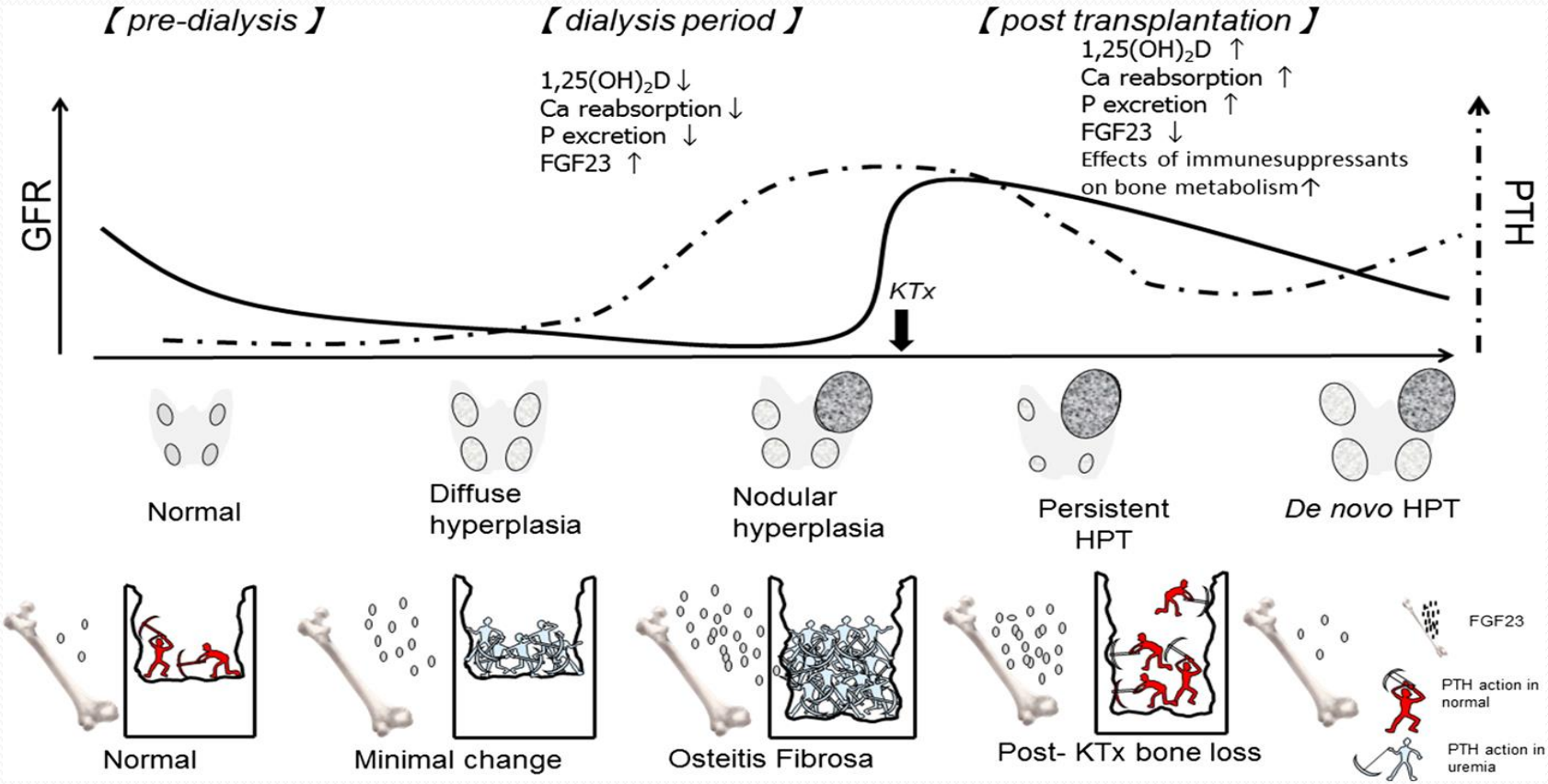
Management of Post.transplant Hyperparathyroidism

Continue…

- Persistent PT-HPT has been associated with increased risk of bone fractures, increased mortality and decreased allograft survival .

Management of Post.transplant Hyperparathyroidism



Management of Post.transplant Hyperparathyroidism

- After kidney transplantation, bone resistance to PTH diminishes, allowing persisting hyperphosphatemia to cause a sudden increase in bone turnover.

- As a result, bone density tends to decrease in the early post-transplant period.

Management of Post.transplant Hyperparathyroidism

Pre.transplant Management of Secondary Hyperparathyroidism:

- Proper management of SHPT prior to transplantation can minimize PT-HPT and its complications of hypercalcemia and hypophosphatemia.

- We generally prefer a pre-transplant (PTX) removed as this will lead to marked bone healing and increased BMD and obviates the need for cinacalcet post-transplant.

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Management of Post.transplant Hyperparathyroidism

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Medical Management and TreatmentOptions of Persistent Post.transplant:

- Hyperparathyroidism Treatments for persistent post-transplant hyperparathyroidism include :
  - vitamin D
  - calcimimetics.
  - parathyroidectomy

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Management of Post.transplant Hyperparathyroidism

Continue…

Use of Vitamin D and its Analogues:

- calcitriol, has been shown to suppress PTH posttransplantation.

- However vitamin D use is limited by its capacity to produce hypercalcemia similar to the pre-transplant period.

Management of Post.transplant Hyperparathyroidism

Continue…

Calcimimetics:

- cinacalcet causes rapid reductions in the calcium and PTH levels in transplant recipients as well.

- Cinacalcet promotes urinary calcium excretion and increases the risk of nephrocalcinosis and a subsequent decrease in renal function

Management of Post.transplant Hyperparathyroidism

SURGICAL PARATHYROIDECTOMY:

- The subtotal parathyroidectomy is the standard treatment, although currently it has been replaced by the calcimimetic cinacalcet.

- some experts prefer early surgical intervention, while others recommend waiting for approximately one year for spontaneous resolution of mild to moderate hyperparathyroidism before therapeutic intervention

Management of Post.transplant Hyperparathyroidism

Continue…

- It is expected that persistent hypoparathyroidism after parathyroidectomy might exacerbate low turnover bone disease.

- A more flexible and reversible control of hyperparathyroidism can be achieved by medical treatment with calcimimetics.

Management of hypercalcemia after renal transplantation

- Hypercalcemia is frequently found in patients with a
- functioning renal allograft, with prevalence ranging between 5% and 66%

- although severe hypercalcemia

  (total calcium > 12mg/dl) is quite exceptional.

Management of hypercalcemia after renal transplantation

CAUSES OF HYPERCALCEMIA:

- Studies showed that high serum PTH values were the main predictorof post-transplantation hypercalcemia.

- withdrawing cinacalcet after RT resultsin high PTH levels immediately after transplantation, and consequently, hypercalcemia in a high number of patients.

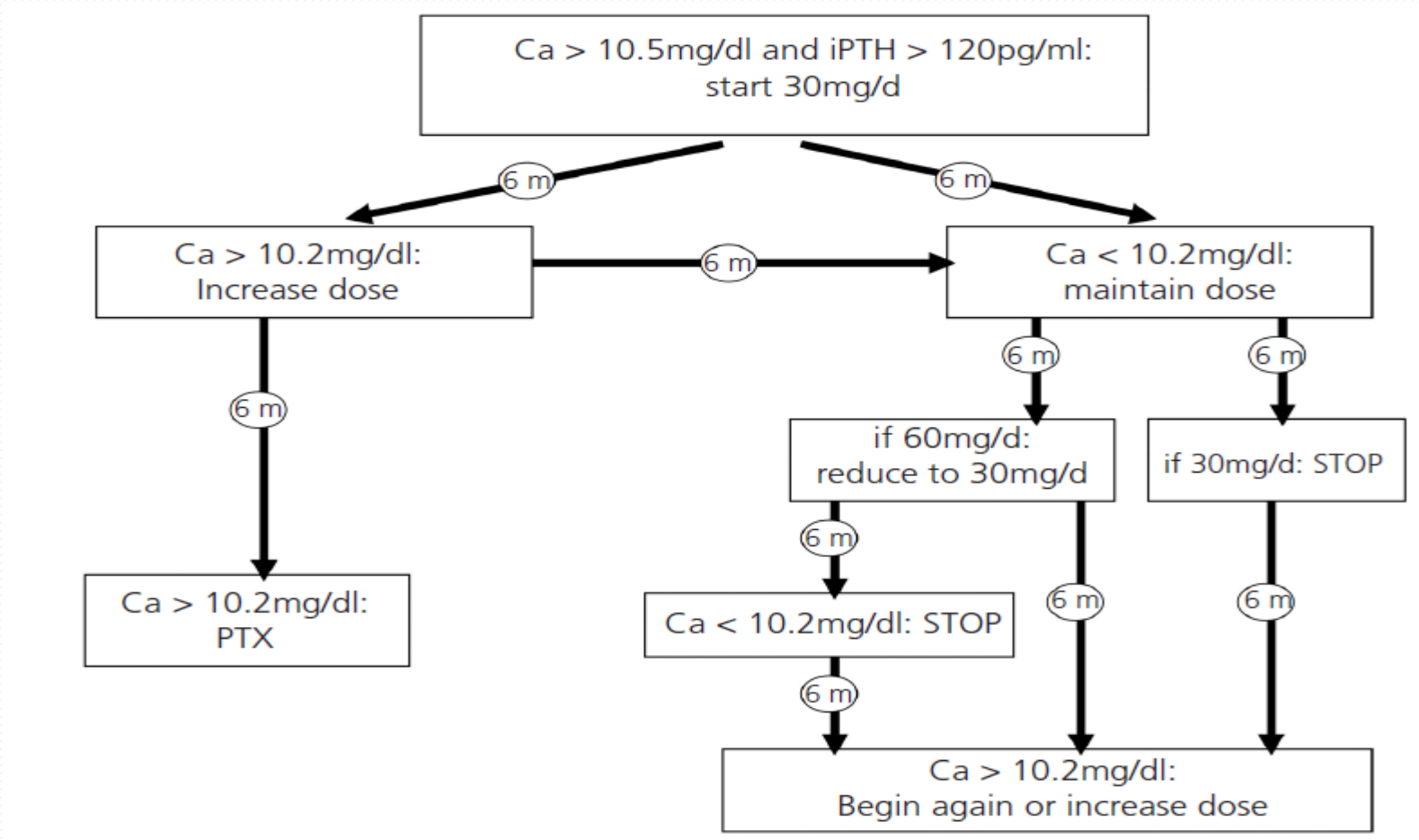
Management of hypercalcemia after renal transplantation

CONSEQUENCES OF HYPERCALCEMIA:

- Hypercalcemia, through a vasoconstriction mechanism may impair renal graft function, both acutely and chronically.

- It may also cause tubulointerstitial calciications that may have a negative inluence on long-term graft survival.

- MANAGEMENT OF POST-TRANSPLANTATION HYPERCALCEMIA




Thank
You!