CKD-MBD after renal transplantation

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Complicatons of CKD-MBD after renal transplantation (KTx)

- Skeletal deformities, e.g. genu valgus/ varum
- Bone pain
- Fractures (fracture risk 140fold increased compared to general population)
- Osteonecrosis / osteoporosis
- Impaired bone mineralization (up-to 35%)
- Growth failure
- Ectopic (vascular) calcifcations, arterial stiffness
- Left ventricular hypertrophy / dysfunction

Haffner D et al, Curr Opin Pediatr 2014; Sgambat K et al, Fronierts in Pediatrics 2014; Helenius I et al JBMR 2006
KDIGO 2017 Clinical Practice Guideline Update on CKD-MBD, Kidney Int 2017

CKD-MBD after KTx: contributing factors:

- Preexisting renal osteodystrophy / CV changes
- Immunosuppression (steroids, CNI)
- Alterations in PTH / vitamin D / FGF23 axis
- Changes in mineral metabolism (phosphate↓, magnesium↓)
- Acidosis
- Unhealthy diet
- Reduced physical activity, muscle deficits
- Impaired graft function (reduced eGFR, acidosis)

Haffner D et al, Curr Opin Pediatr 2014; Sgambat K et al, Fronierts in Pediatrics 2014
KDIGO 2017 Clinical Practice Guideline Update on CKD-MBD, Kidney Int 2017

Steroids

- ✓ Promote osteonecrosis (femoral head)
- ✓ Promote osteoporosis, cortical thinning ➔ increased fracture risk
- ✓ Impair growth by reducing Ca absorption, osteoblast proliferation & IGF1 synthesis
- ✓ Promote obesity & hypertenison

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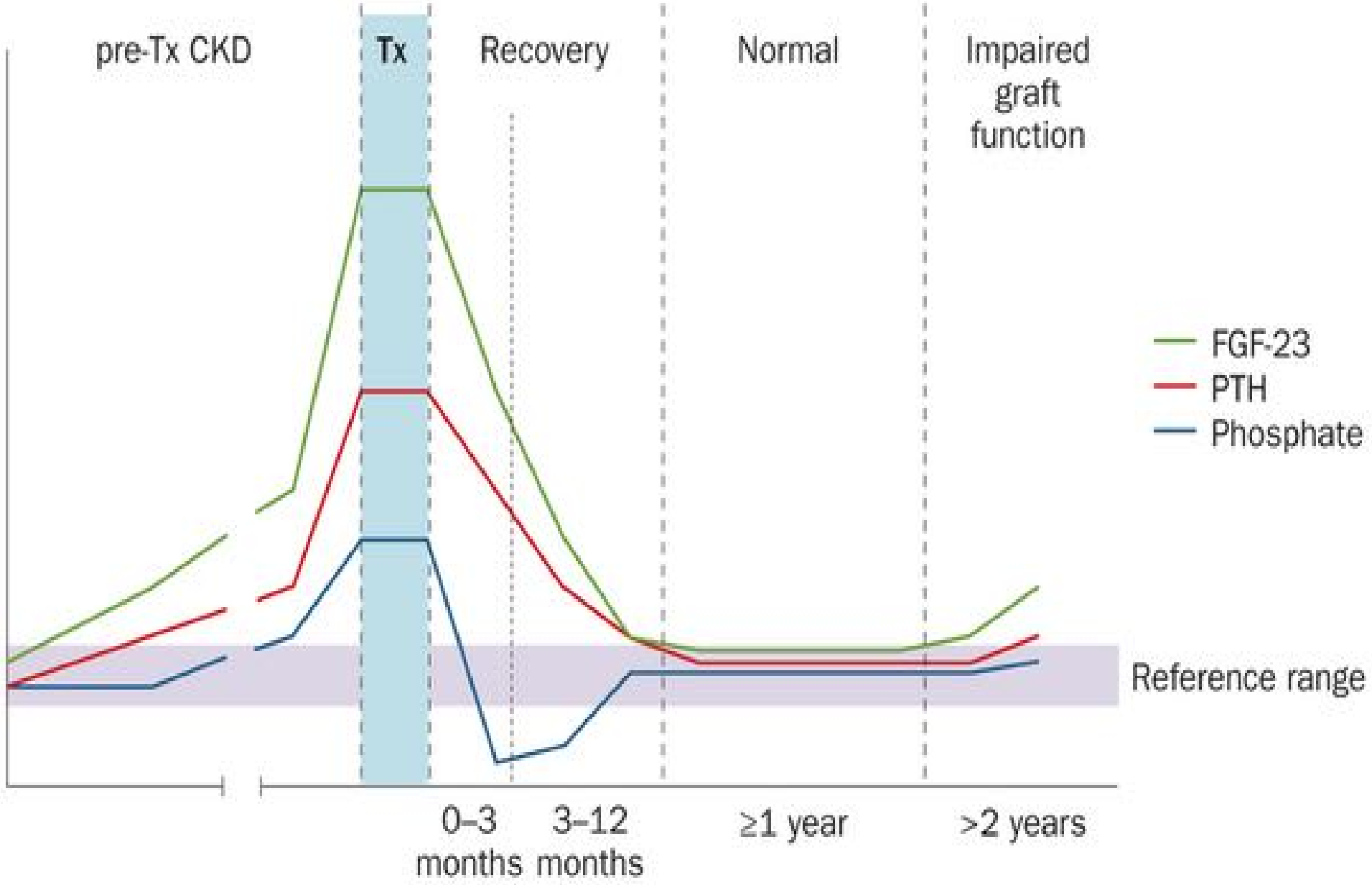


Baia LC et al, Nat Rev Nephrol 2015; 11: 656-666

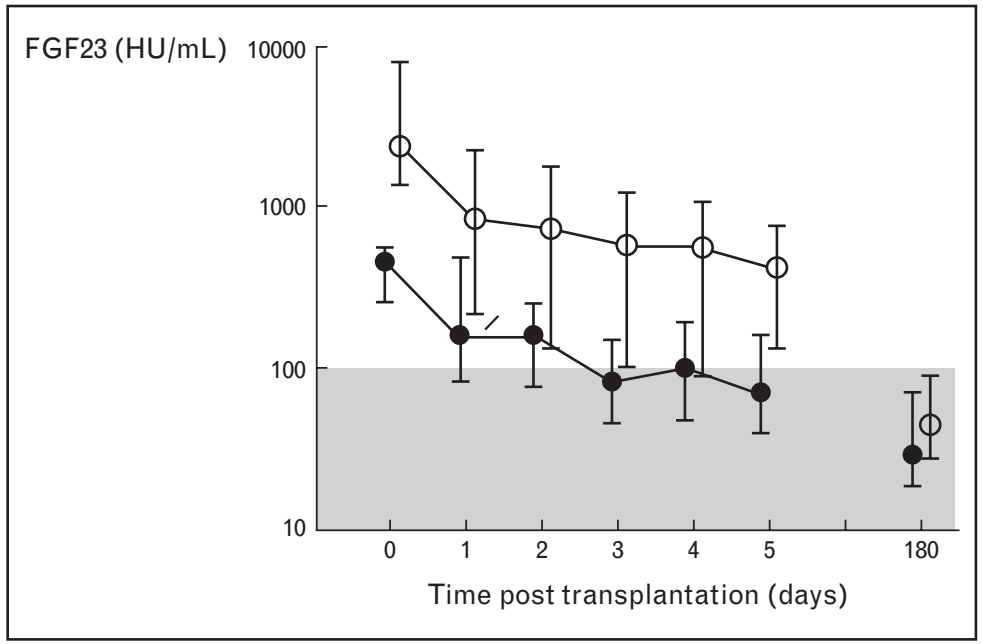
Increased PTH, FGF23, and hypophosphatemia

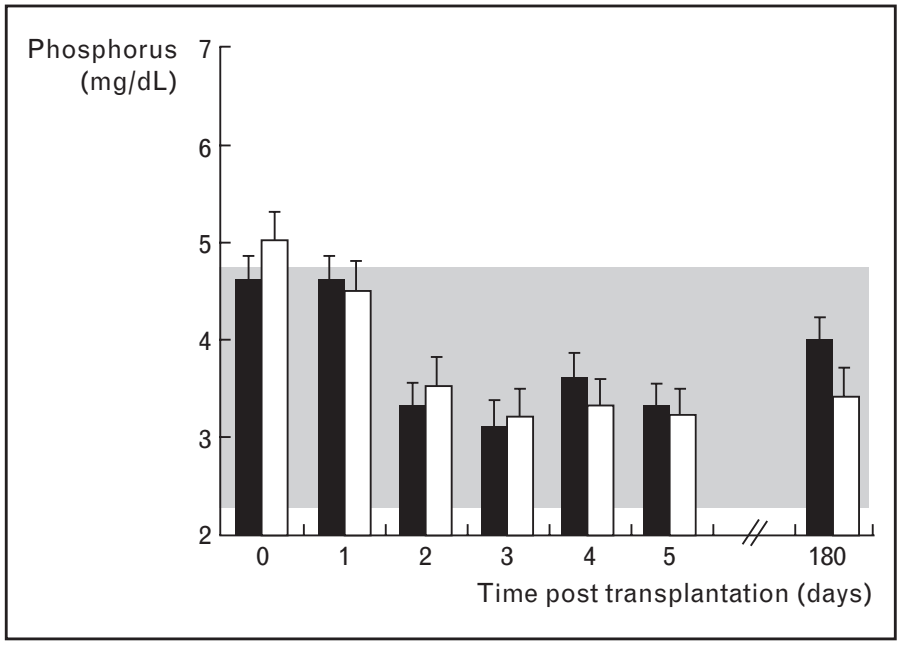
- Persisting elevated PTH levels in case of severe 2nd or tertiary hyperparathyroidism prior to KTx
- Pretransplant elevation of FG23 are the strongest predictor of post-transplant elevation of FGF23, and FGF23 levels independently predict hypophosphatemia and low 1,25 vitamin D levels.
  - Consequence: decreased osteoblast activity and progressive bone demineralization
- Chronic allograft nephropathy* may result in elevated FGF23 & PTH-levels

* interstitial fibrosis and tubular atrophy (IF/TA), without evidence of any specific etiology

Wesseling-Perry K et al, Ped Nephrol 2013; Haffner D et al, Curr Opin Pediatr 2014
Sgambat K et al, Fronierts in Pediatrics 2014

Course of plasma FGF23 and phosphorus levels after pediatric KTx

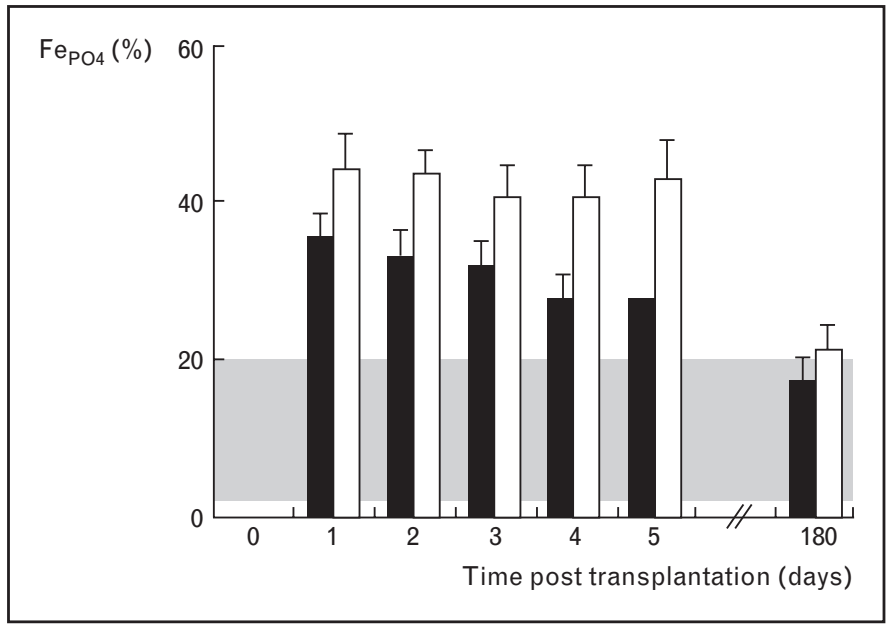


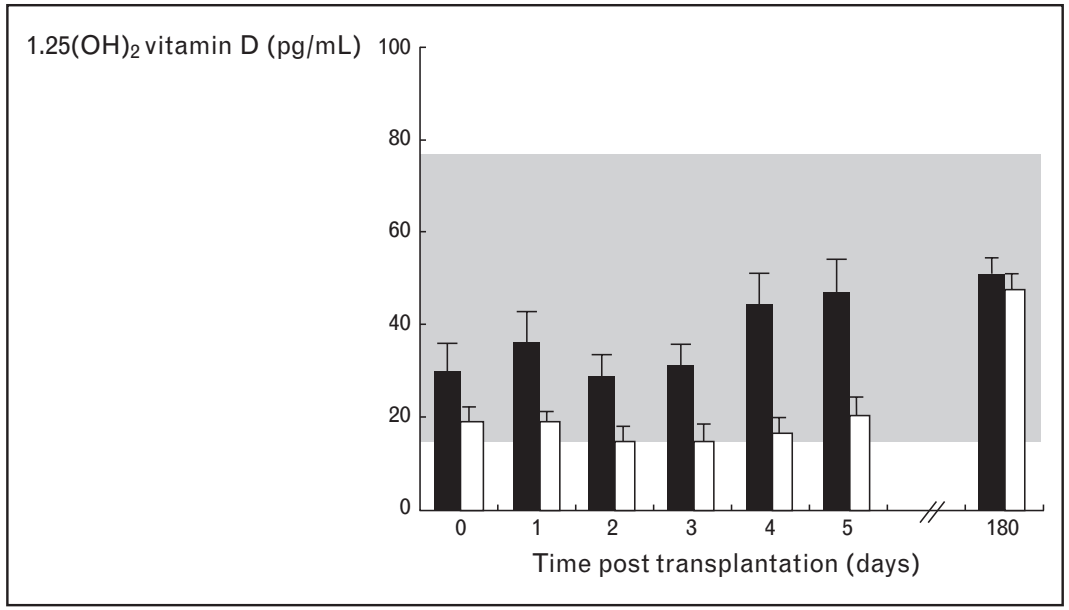


FGF23 pretransplant values

- above the median
- below the median

Course of fractional excretion of phosphate and circulating 1,25 vitamin D levels in pediatric KTx



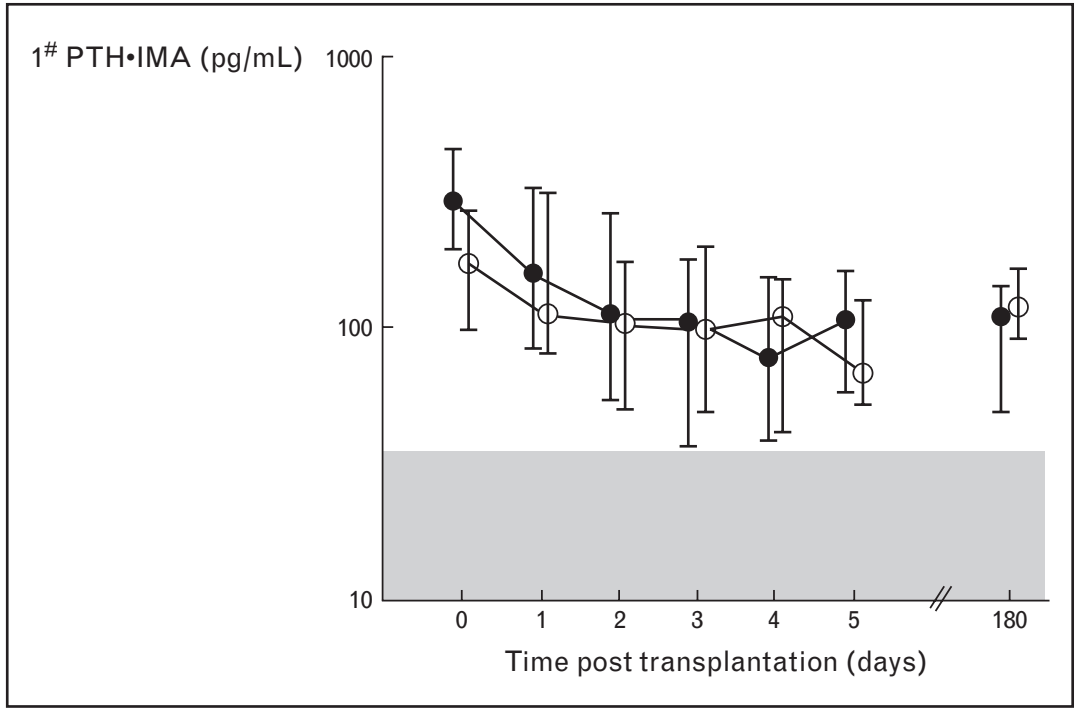


FGF23 pretransplant values

- above the median
- below the median

Wesseling-Perry K et al, Ped Nephrol 2013; 28: 2207-2215

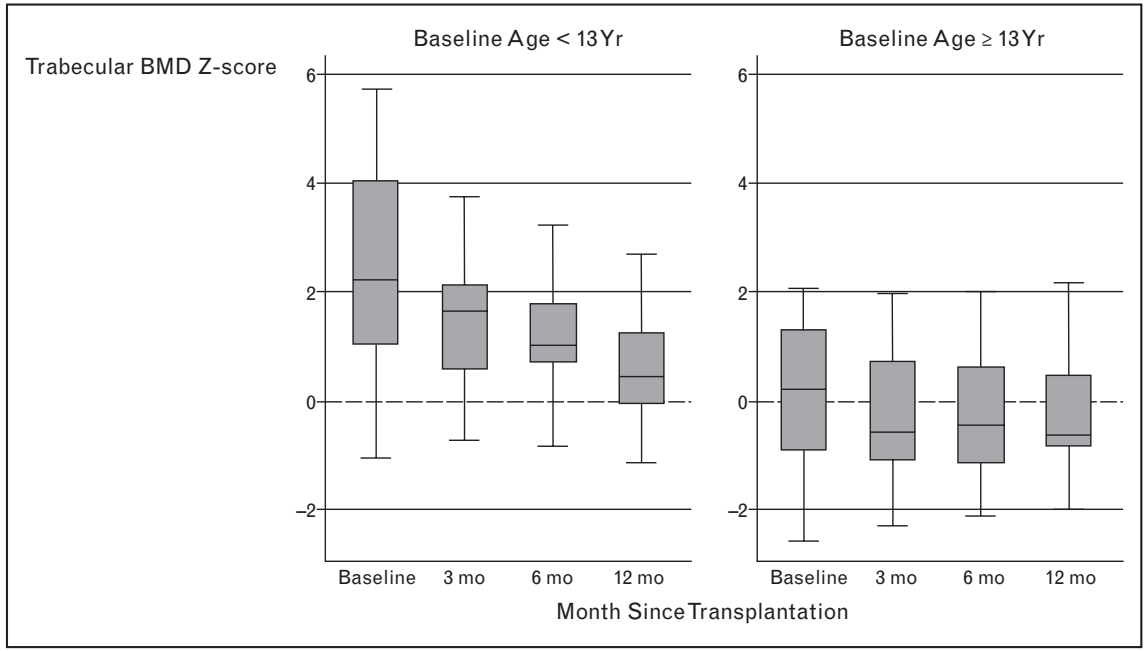
Course of PTH levels in pediatric KTx



FGF23 pretransplant values

- ○ above the median
- • below the median

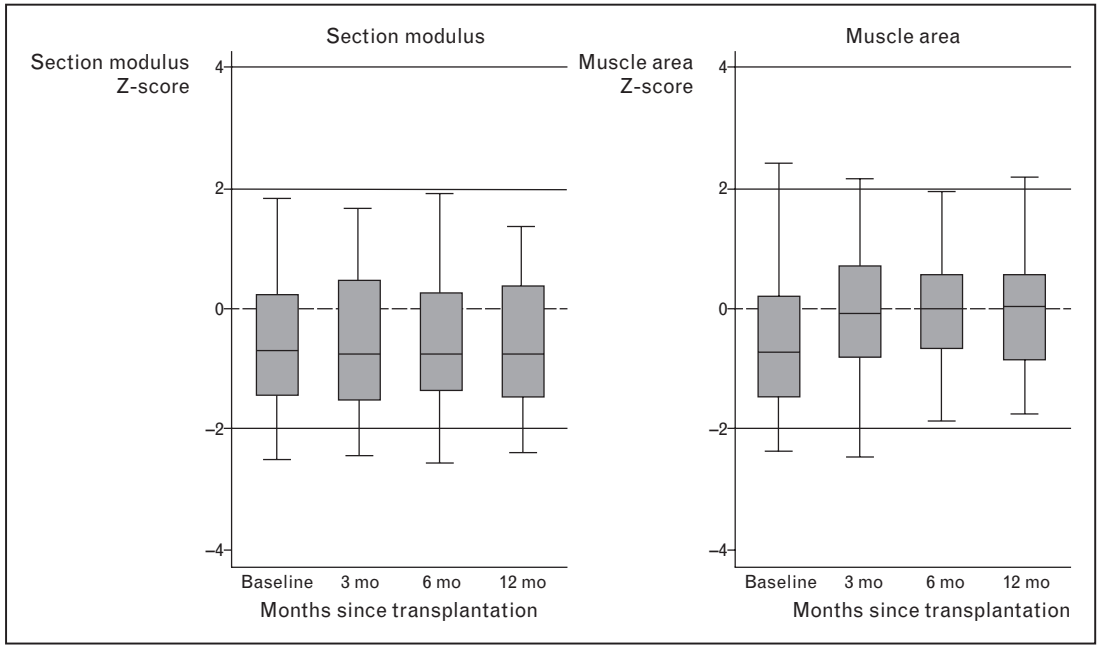
Trabecular BMD Z-scores assessed by pQCT after transplantation according to age at KTx



Elevated trabecular BMD Z-score probably due to 2nd HPT
PTH stimulates the transformation of metaphyseal spongiosa to diaphyseal spongiosa

Terpstra AM et al, J Am Soc Nephrol 2012; 23: 715-726

Section modulus and muscle area Z-scores assessed by pQCT after pediatric KTX



10% fractures within 6 months
Section modulus is a measure of bone strength and related to cortical thickness
Persistent cortical thinning due to steroids?

Cardiovascular comorbidity & risk factors in pediatric KTx patients

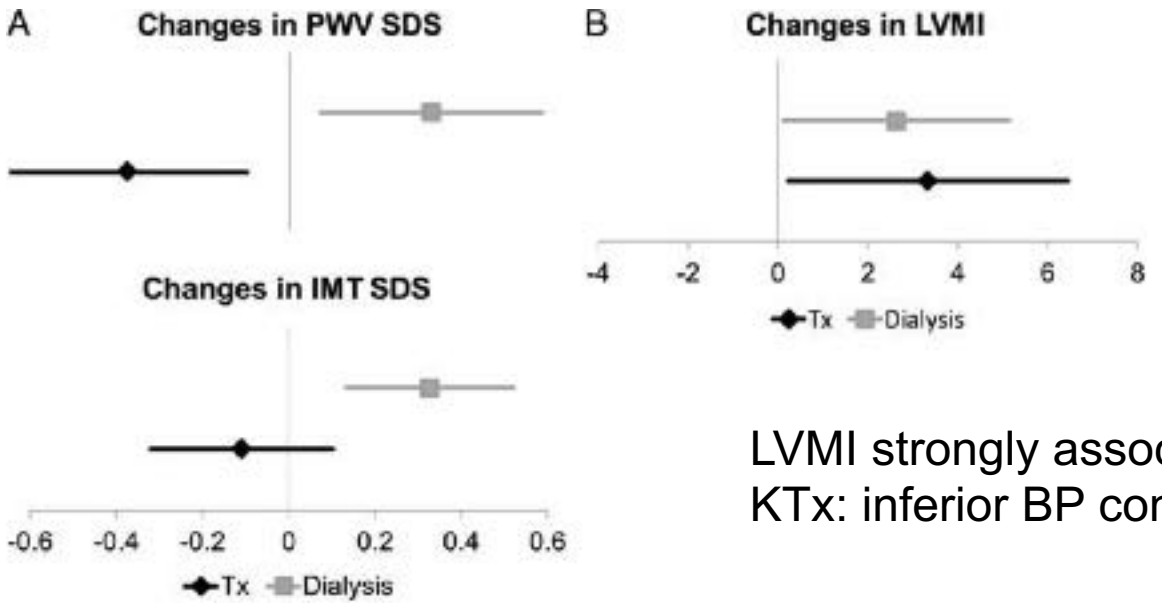
- Uncontrolled / untreated hypertension (> 90 Pct.): 41%
- Left ventricular hypertrophy: 43%
- Arterial stiffness (increased PWV): 22%
- Atherosclerosis (increased cIMT): 58%
- Obesity: 17%
- Elevated LDL cholesterol: 34%
- Reduced HLD: 28%

Major risk factors associated with CV target organ damage in pediatric KTx patients

- Hypertension
- Low eGFR
- Elevated BMI
- Steroids

Borchert-Mörlins B et al, Ped Nephrol 2017; 32: 2143-2145; Schmidt B et al, Transplantation 2018; 102: 484-492

CV endpoints in patients undergoing either preemptive KTx or dialysis as initial RRT



LVMI strongly associated with increased BP
KTx: inferior BP control & larger BMI

FIGURE 2. Corrected means and 95% CI of surrogate cardiovascular endpoints in patients undergoing preemptive dialysis (D) or transplantation (Tx). *A*, Change in PWV SDS (adjusted for PWV SDS before RRT, time interval between assessments, Δheight, Δdiastolic blood pressure SDS) and IMT SDS (adjusted for IMT SDS before RRT, time interval between assessments, Δheight, ΔBMI SDS, number of antihypertensive drugs). *B*, Change in LVMI in $g/m^{2.7}$ (adjusted to LVMI before RRT, time interval between assessments, Δheight, systolic blood pressure SDS).

Assessment of CKD-MBD post KTx

- Clinical assessment: height, signs of rickets, leg bowing, pain (every visit)
- Serum Ca, P, AP, iPTH, 25 OHD (1-12 monthly depending on CKD stage)

CKD stage	Follow-up
Stage 1-3T	Calcium and phosphorus every 6–12 months, PTH at least once, to adapt to the evolution of renal function
Stage 4T	Calcium and phosphorus every 3–6 months, PTH every 6–12 months
Stage 5T	Calcium and phosphorus every 1–3 months, PTH every 3–6 months
Stage 3-5T	Alkaline phosphatase every year, and more frequently in case of hyperparathyroidism
Stage 1-5T	25(OH)-Vitamin D to measure on a regular basis, to define depending on the baseline levels. In all cases, a vitamin D deficiency should be corrected.

CKD, chronic kidney disease.

Assessment of CKD-MBD post KTx

- Clinical assessment: height, signs of rickets, leg bowing, pain (every visit)
- Serum Ca, P, AP, iPTH, 25 OHD (1-12 monthly depending on CKD stage)

These parameters should be considered together with particular attention to trends in values

KDIGO CKD-MBD Guideline Update 2017

Assessment of CKD-MBD post KTx

- Clinical assessment: height, signs of rickets, leg bowing, pain (every visit)
- Serum Ca, P, AP, iPTH, 25 OHD (1-12 monthly depending on CKD stage)

- X-ray of left wrist (in case of persisting severe sHPT, impaired graft function)
- Bone histomorphometry: if knowledge of the type of renal osteodystrophy will impact treatment decissions
- DXA (BMD): recommended in adults (osteoporosis?)
  no evidence for its use in children
- Clinical studies: pQCT, PWV, cIMT, FGF23 & other novel biomarkers

Management of CKD-MBD post KTx

- Adequate lifestyle: healthy diet, regular physical activity (30 min/day), no smoking
- Correct:
  - Post-transplant hypophosphatemia
  - Hypomagnesemia (CNI)
  - Nutritional Vitamin D deficiency
  - Hyperparathyroidism
  - Acidosis (keep HCO_3 > 22 mEq/L)
  - Hypertension (target: BP < 75 Pct. / < 50 Pct. in case of proteinuria)
- Immunosuppression: keep up graft function, minimize steroid exposure

Haffner D et al, Curr Opin Pediatr 2014; Sgambat K et al, Frontiers in Pediatrics 2014
KDIGO 2017 Clinical Practice Guideline Update on CKD-MBD, Kidney Int 2017

Diet and phosphate / magnesium suppl.

- Provide adequate caloric & protein intake (100% RDA)
- Provide adequate dietary calcium and phosphorus intake (at least 100% RDA)
- Avoid high sodium intake (< 2g/day; hypertension, hypercalciuria, bone formation↓)
- Avoid cola beverages (decreased BMD & increased fracture risk)
- Persistent post-transplant hypophosphatemia:
  - Initiate, high phosphorus diet and oral phosphate supplementation in order to reach low normal levels (for age)
  - Phosphate supplementation may further stimulate renal phosphate wasting
- Magnesium deficiency promotes osteoporosis & PTH resistance
  - Supplement magnesium in case of hyopomagnesemia

Haffner D et al, Curr Opin Pediatr 2014; Sgambat K et al, Frontiers in Pediatrics 2014
KDIGO 2017 Clinical Practice Guideline Update on CKD-MBD, Kidney Int 2017

Native Vitamin D Supplementation in Children with CKD Stages 2-5D

Clinical Practice Recommendations

european society for paediatric nephrology

- **Target:** 25(OH)D **75**-120 nmol/L (**30** - 50 ng/ml)
- Daily supplementation: cholecalciferol (D3) or ergocalciferol (D2)

Intensive replacement phase			
Age	25(OH)D serum (nmol/L)**	Vitamin D supplementation dose (daily)	Monitoring
< 1 year		600 IU / day	- Serum calcium and urinary calcium levels 1-3 monthly based on CKD stage - 25(OH)D level: after 3 months
>1 year*	< 12	8000 IU / day	
	12 - 50	4000 IU / day	
	50 – 75	**2000 IU / day**	
Maintenance phase			
< 1 year	>75***	400 IU / day	- 25(OH)D level: 6-12 monthly
>1 year*		**1000 - 2000 IU /**day based on CKD stage	

* Consider adjusting dose by body size (weight or body surface area); ** To convert nmol/L to ng/ml divide by 2.5
*** If levels remain <75nmol/L, then give doses as per the 'Intensive replacement' schedule for a further course of intensive replacement & recheck levels

PTH

- PTH levels should be maintained within the target range based on the stage of CKD.
- Measures:
  1. Supplementation of native vitamin D
  2. Calcitriol or Alfacalcidol

- **Apply minimal PTH suppressive dosage !**

➢ **Appreciate trends in Ca, P, AP, PTH !**

Haffner D et al, Curr Opin Pediatr 2014; Sgambat K et al, Fronierts in Pediatrics 2014
KDIGO 2017 Clinical Practice Guideline Update on CKD-MBD, Kidney Int 2017

Searching the optimal PTH target…

	CKD Stage	GFR (ml/min/1.73m²)	iPTH (pg/mL)	
KDOQI:	2	60-89	35-70	**1x**
	3	30-59	35-70	**1x**
	4	15-29	70-110	1-2x
	5	<15, dialysis	150-300	3-5x
KDIGO:	5	<15, dialysis	120-540	2-9x
Europe:	4	15-29	120-180	**2-3x**
	5	<15, dialysis	120-180	**2-3x**
IPNN:	5	PD	100-200	**1.7-3x**

www.kidney.org/professionals/KDOQI/guidelines/ ; KDIGO CKD-MBD guideline, Kidney Int 2017
Klaus et al, Pediatr Nephrol 2006; Haffner et al Ped Nephrol 2013

Parathyroidectomy

- Persistant severe, therapy-refractory sHPT:
  - radiological signs
  - hypercalcemia
- (Parathyroid gland > 0.5 cm^3 or diameter > 1.0 cm)

✓ Subtotal PTX and/or autotransplantation

Haffner D et al, Curr Opin Pediatr 2014; Sgambat K et al, Fronierts in Pediatrics 2014
KDIGO 2017 Clinical Practice Guideline Update on CKD-MBD, Kidney Int 2017

Steroids

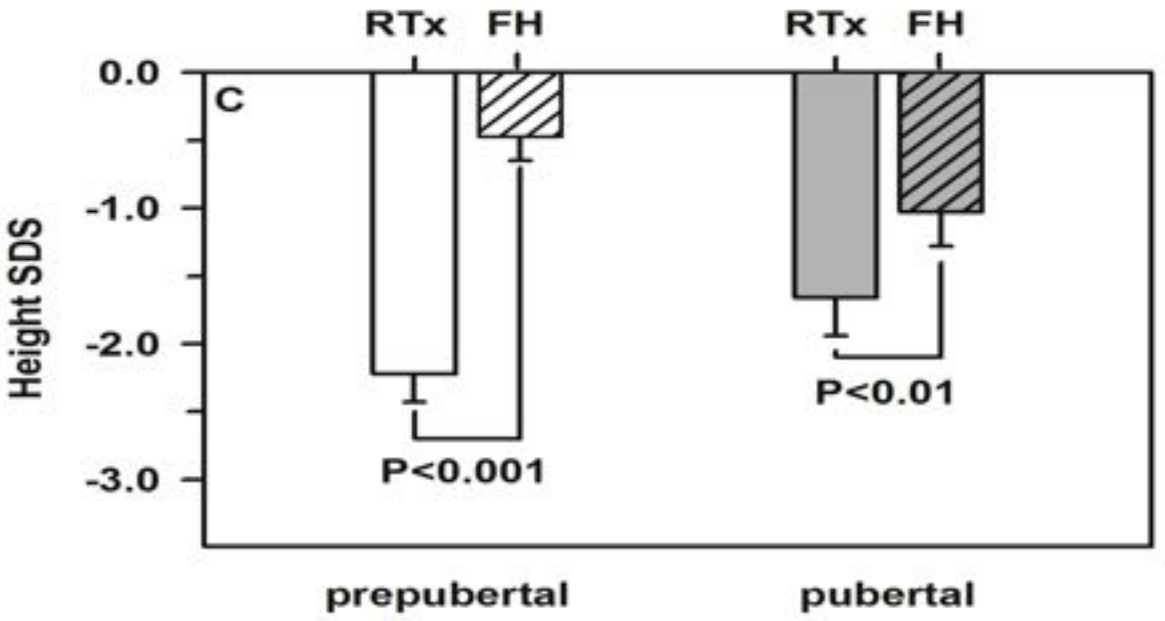
Protocols to reduce steroid exposure after transplantation

- ✓ Complete steroid avoidance*
- ✓ Early steroid withdrawal* < 7 days
- ✓ „Intermediate“ withdrawal* > 7days < 1 year
- ✓ Late withdrawal > 1 year

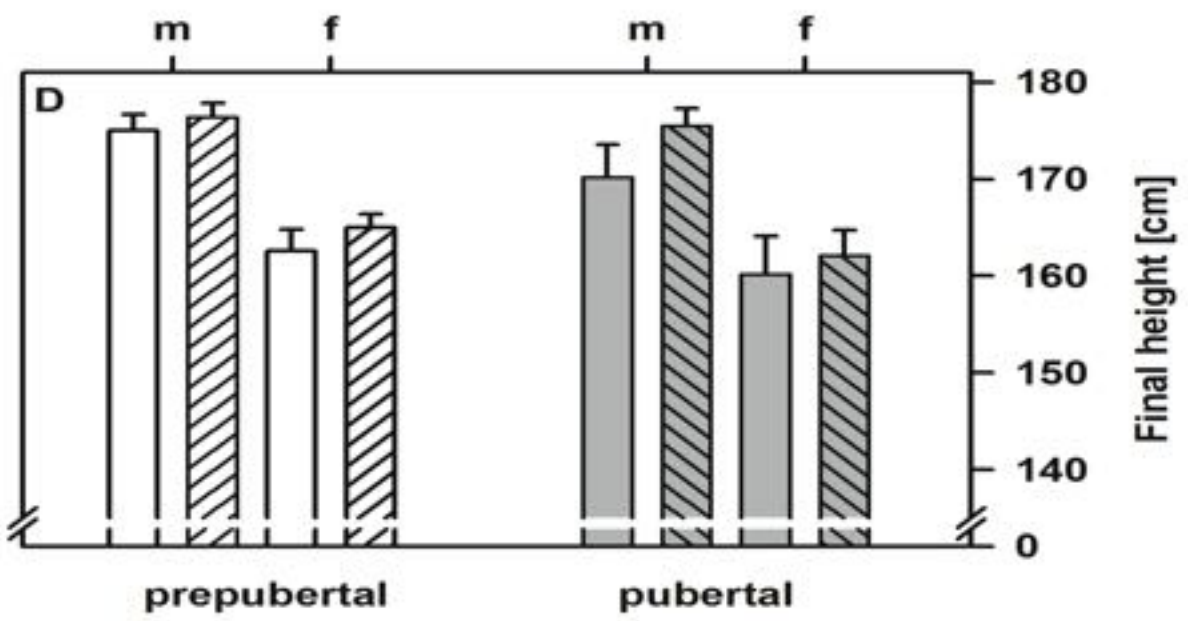
*Calcineurin inhibitor (CyA/Tac) + MMF / everolimus
+ induction: basiliximab / daclizumab (complete steroid avoidance)

Normal adult height after „intermediate“ (6 mo.) steroid-withdrawal in pediatric KTX

Height at KTx vs. final height

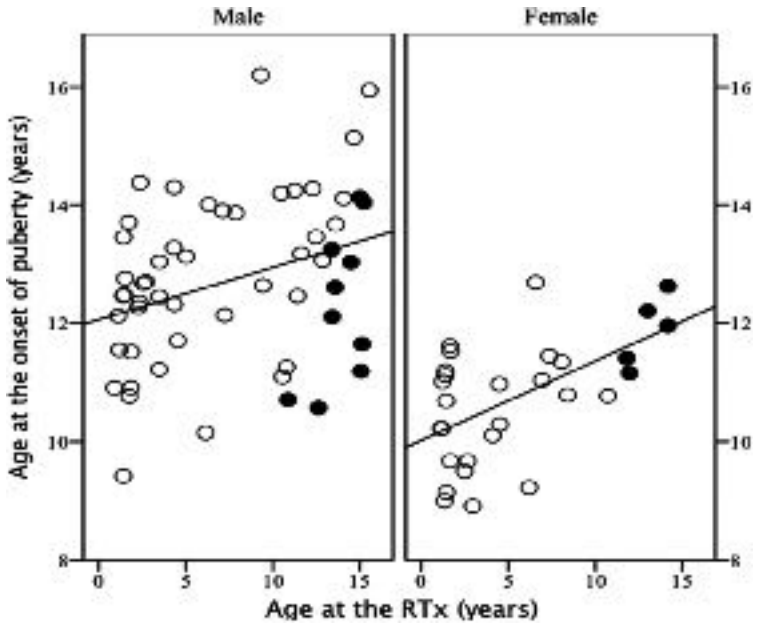


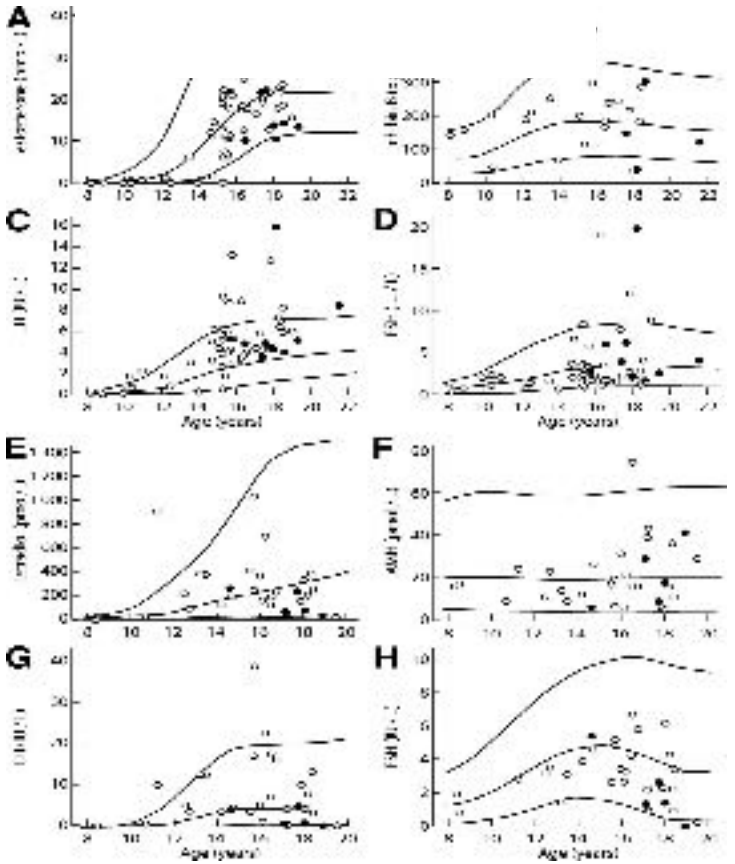
Final height vs. target height



Klare *et al*, Transplant Int 2012; 334:56

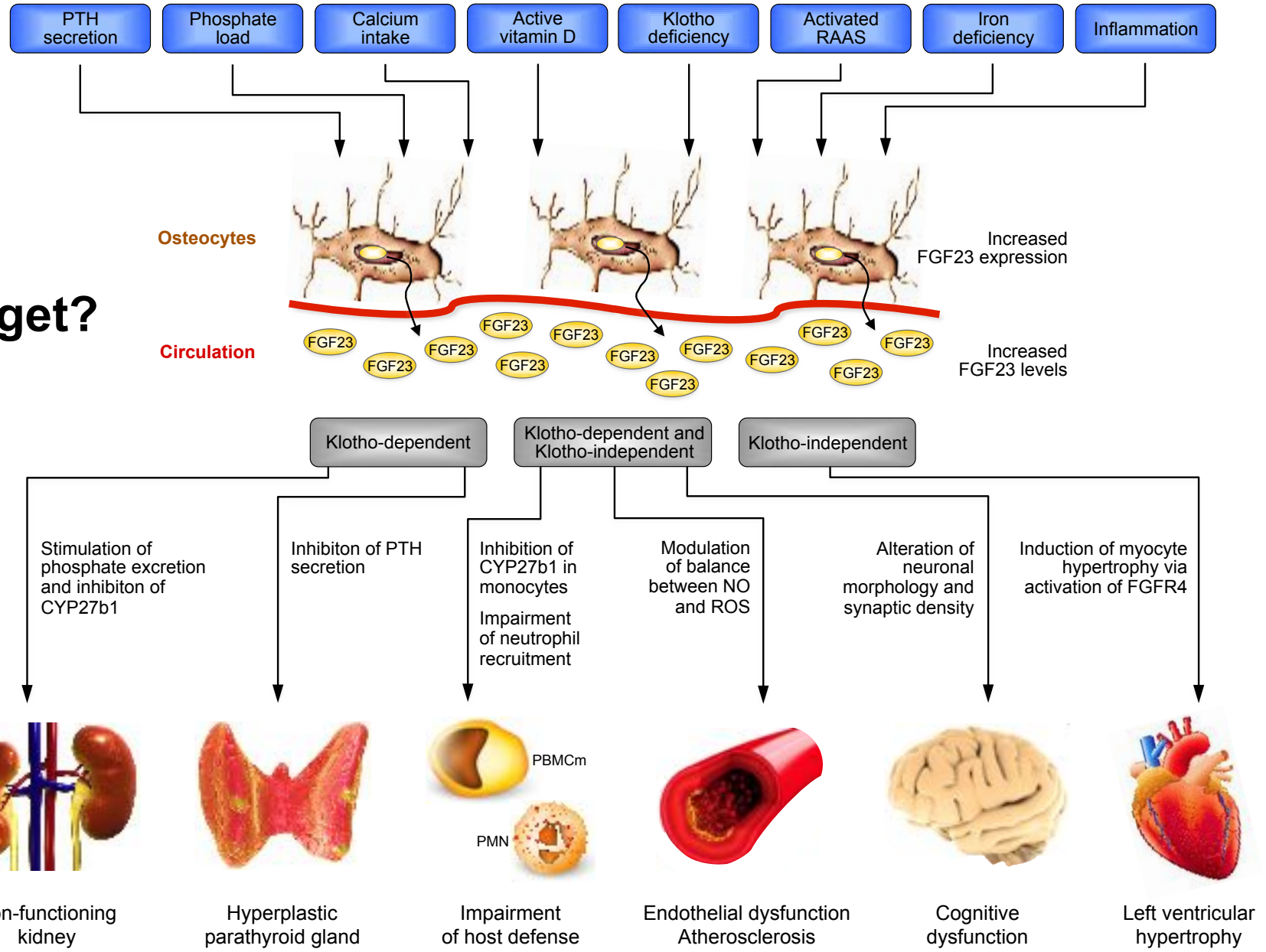
Normal sexual Maturation in Adolescents after KTx





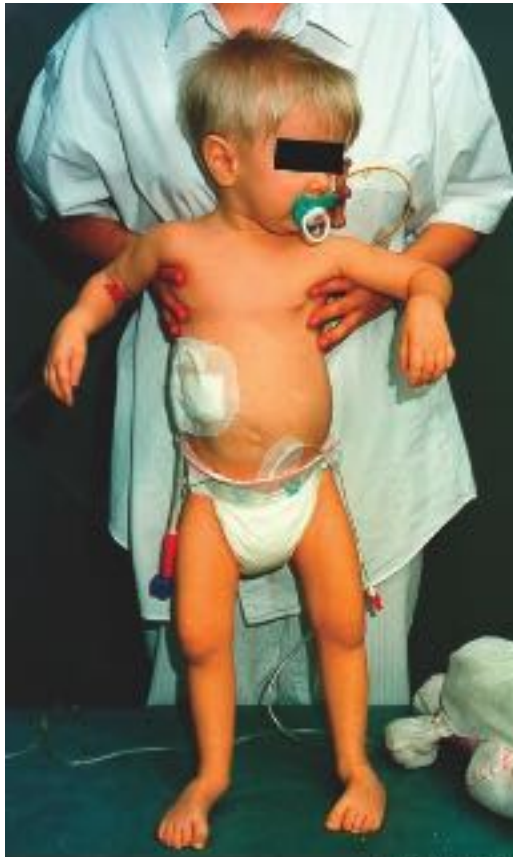
Tainio *et al*, Transplantation 2011

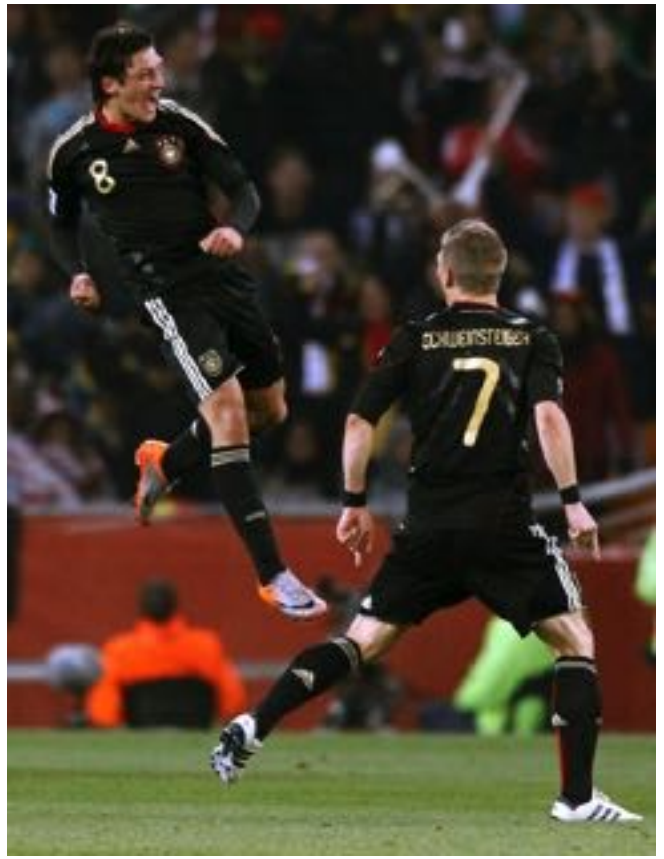
FGF23:
The future target?



Haffner & Leifheit-Nestler, *Pediatr Nephrol 2017*

Adequate management of CKD-MBD after KTx is a challenge but not a miracle !





Thank you for your attention

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CKD-MBD post KTx: Question 1

What is not a typical clinical feature of posttransplant CKD-MBD?

a. Bone pain
b. Delayed sexual maturation
c. Vascular calcifications
d. Fractures

CKD-MBD post KTx: Question 2

Posttransplant CKD-MBD is not due to

a. Steroid treatment
b. Reduced graft function
c. Reduced Klotho levels
d. Preexisting renal osteodystrophy

CKD-MBD post KTx: Question 3

Management of posttransplant CKD-MBD mainly focuses on

a. Maintenance of of regular physical activity
b. High sodium intake
c. Preservation of graft function
d. Correction of vitamin D deficiency

Which answer is wrong?