CHAPTER 8.2 CKD mineral and bone disorder post-transplant

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1 Causes and clinical spectrum of post-transplant CKD-MBD

Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) is highly prevalent in paediatric kidney transplant recipients, even in those with a good allograft function. The main contributing factors include pre-transplant CKD-MBD, graft function and the side effects of immunosuppressive drugs. Prior to transplantation, and starting from the early stages of CKD, every effort should be made to optimise bone health, but severe pre-transplant CKD-MBD is not a reason to delay or withhold transplantation. The clinical picture of post-transplant CKD-MBD is broad and includes bone pain, skeletal deformities, fractures, growth failure and ectopic vascular calcification.

a. First 3 months post-transplant

The earliest alteration in the pathogenesis of pre-transplant CKD-MBD is elevated levels of the phosphaturic hormone fibroblast growth factor 23 (FGF23), followed by low levels of 1,25-dihydroxyvitamin D, hypocalcaemia, hyperparathyroidism, and hyperphosphatemia [1]. During the recovery phase post-transplant, elevated levels of FGF23 and parathyroid hormone (PTH) often persist for several months, which in the presence of restored kidney function may cause

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hypophosphatemia and promote impaired bone mineralisation. In a retrospective analysis of 1,210 paediatric transplant recipients, 36% had hypophosphatemia 4 weeks post-transplant. There was no association with allograft dysfunction [2]. In addition, *hypomagnesemia* may occur as a side effect of tacrolimus due to tubular wasting.

Given that no adverse patient- or allograft outcomes have been reported to date in paediatric kidney transplant recipients with mild or moderate hypophosphatemia or hypomagnesemia, supplementation should be considered mainly in severe or symptomatic cases, bearing in mind that phosphate and magnesium supplements may cause diarrhoea and further reduce drug absorption.

b. 3 months post-transplant and beyond

After the recovery period CKD-MBD parameters often remain within reference ranges, although high PTH levels have been reported even in patients with good allograft function. At 1 year post-transplant, 56% of patients with an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 had elevated PTH levels, and the degree of hyperparathyroidism was associated with allograft dysfunction [2]. In addition, higher PTH levels have been reported in kidney transplant recipients than in pre-transplant patients with a similar eGFR [2, 3] (Table 1).

Table 1 Comparison of pre- and post-transplant PTH levels in different CKD stages

Pre-transplant	**Overall**	**Stage 2 (eGFR ≥ 60 ml/min per 1.73 m^2)**	**Stage 3a (eGFR 45–59 ml/min per 1.73 m^2)**	**Stage 3b (eGFR 30–44 ml/min per 1.73 m^2)**	**Stage 4 (eGFR 15–29 ml/min per 1.73 m^2)**
Plasma iPTH, pg/ml	51 [30, 84]	37 [26, 54]	48 [26, 70]	55 [33, 95]	74 [47, 181]
Post-transplant					
Plasma iPTH, pg/ml		55 [38, 81]	62 [40, 90]	81 [52, 122]	

Data is given as median and interquartile range; iPTH, intact PTH

In 1,237 children included in the European Society for Paediatric Nephrology (ESPN) and European Renal Association (ERA) registry, abnormal serum phosphate levels were found in 25% of patients (14% hypophosphatemia and 11% hyperphosphatemia), and serum phosphate levels were inversely associated with eGFR. Serum phosphate levels above the recommended targets were associated with a higher risk of graft failure independent of eGFR [4].

2 Evaluation of post-transplant CKD-MBD

a. Clinical evaluation

Points to consider:

- Monitor height (length at age < 2 years), weight, skeletal deformities, and history for bone pain and fractures.
- The frequency of monitoring depends on the age, graft function, and degree of skeletal abnormalities at the time of kidney transplantation and during follow-up.

b. Laboratory evaluation

Points to consider:

- Monitor serum calcium, phosphate and alkaline phosphatase levels using age- and/or sex-specific normal ranges as well as PTH and 25-hydroxyvitamin D.
- Use trends in serum biomarkers considered together, rather than individual laboratory values, to guide therapeutic decisions.
- Tailor the frequency of monitoring to the time since kidney transplantation, the presence and severity of CKD-MBD, age, allograft function, concomitant medications, and in the early post-transplant period, also the degree of pre-transplant CKD-MBD
- Do not routinely measure 1,25-dihydroxyvitamin D levels

c. Imaging

Evidence for radiological evaluation and bone biopsy in the management of mineral bone disease in paediatric kidney transplant patients is limited.

Points to consider:

- Consider performing X-rays when the results are expected to impact on treatment decisions, i.e. in children with bone pain, suspected fractures or slipped epiphyseal dislocations, suspected avascular necrosis, to assess skeletal maturity, and in children with genetic diseases with specific bone involvement (e.g. oxalosis).
- Imaging techniques such as dual-energy X-ray absorptiometry (DXA), peripheral quantitative computed tomography (pQCT), high-resolution pQCT (HR-pQCT), magnetic resonance imaging (MRI) and ultrasound should be reserved for exceptional clinical cases and research questions.
- The risk-benefit ratio of these procedures should always be considered, particularly with regard to radiation exposure.
- Bone biopsies should be considered in paediatric transplant recipients only in rare, selected cases when clinical and biochemical findings do not explain the underlying bone disease, e.g. severe bone deformity or pain, low energy fractures, persistent hypercalcemia or hypophosphatemia, despite optimisation of treatment. Histomorphometric analysis should only be performed in centres with experience in interpreting paediatric bone biopsies.

3 Management of post-transplant CKD-MBD

a. Nutrition

Beyond 3 months from kidney transplantation maintaining serum calcium and phosphate within the normal range for age is recommended. This can be achieved by adequate dietary calcium and phosphate intake and supplementation if required. While many aspects of the diet can be liberalised after kidney transplantation, particular attention should be paid to sodium and energy intake. Transplant recipients are at high risk of hypertension, so it is important to maintain dietary sodium intake within the recommendations of the Chronic Disease Risk Reduction as a starting point, and to reduce it further in those with hypertension. In addition, renal and extra-renal sodium losses, as well as the so-

dium intake from medication, need to be taken into account when recommending a dietary sodium intake. In particular, sodium intake from processed and ultra-processed foods needs to be restricted.

In addition, patients tend to gain weight rapidly after kidney transplantation; so energy consumption should be carefully managed to avoid obesity and its associated complications.

b. Vitamin D - native and active

The prevalence of vitamin D deficiency persists after transplantation. The age- and CKD stage-specific recommendations for native vitamin D supplementation are considered appropriate for children after kidney transplantation [5]. Similarly, active vitamin D (alfacalcidol or calcitriol) may be used to control hyperparathyroidism or hypocalcaemia, using comparable CKD stage-specific recommendations [6].

c. Calcimimetics

Calcimimetics are not approved for use in children after kidney transplantation, but may be considered on an off-label basis in those with severe and persistent hyperparathyroidism with associated hypercalcaemia [7]. This situation may occur in those with severe pre-transplant MBD, or in those with a failing allograft.

d. Antiresorptive agents

Antiresorptive agents are not recommended in children after kidney transplantation, but may be considered in the setting of severe hypercalcaemia that persists despite withdrawal of all sources of calcium and vitamin D. Short-acting bisphosphonates such as pamidronate are preferred to long-acting bisphosphonates. In rare situations where hypercalcaemia is thought to be secondary to severe bone demineralisation, such as in patients with prolonged bed rest, denosumab may be considered.

4 Glucocorticoid-sparing immunosuppression and bone health

The benefits of glucocorticoid-sparing immunosuppression in terms of statural growth are described in Chapter 5.1. Glucocorticoid exposure is also associated with reduced bone mineral density (BMD) and increased fracture incidence, although data in paediatric patients are scarce. In a prospective longitudinal analysis of 58 recipients, Terpstra et al. reported a significant decrease in trabecular BMD after transplantation associated with greater glucocorticoid exposure, while cortical BMD increased significantly in association with greater glucocorticoid exposure and greater decreases in PTH levels [8]. Another study by Helenius et al. reported an unusually high fracture rate in 75 out of 196 paediatric solid organ transplant recipients with a 5-year follow-up. While all patients were treated with glucocorticoids, there was no association between fracture incidence and the cumulative glucocorticoid dose [9]. Overall, glucocorticoid-sparing immunosuppressive protocols should be favoured in children after kidney transplantation to improve bone health, taking into account local standards and the patient's risk profile for graft rejection including medication adherence, previous rejection and donor-specific HLA antibodies.

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