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EDUCATIONAL REVIEW

CKD-MBD post kidney transplantation

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Abstract

Complications of chronic kidney disease-associated mineral and bone disorders (CKD-MBD) are frequently observed in pediatric kidney transplant recipients and are associated with high morbidity, including growth failure, leg deformities, bone pain, fractures, osteonecrosis, and vascular calcification. Post-transplant CKD-MBD is mainly due to preexisting renal osteodystrophy and cardiovascular changes at the time of transplantation, glucocorticoid treatment, and reduced graft function. In addition, persistent elevated levels of parathyroid hormone (PTH) and fibroblast growth factor 23 may cause hypophosphatemia, resulting in impaired bone mineralization. Patient monitoring should include assessment of growth, leg deformities, and serum levels of calcium, phosphate, magnesium, alkaline phosphatase, 25-hydroxyvitamin D, and PTH. Therapy should primarily focus on regular physical activity, preservation of transplant function, and steroid-sparing immunosuppressive protocols. In addition, adequate monitoring and treatment of vitamin D and mineral metabolism including vitamin D supplementation, oral phosphate, and/or magnesium supplementation, in case of persistent hypophosphatemia/hypomagnesemia, and treatment with active vitamin D in cases of persistent secondary hyperparathyroidism. The latter should be done using the minimum PTH-suppressive dosages aiming at the recommended CKD stage-dependent PTH target range. Finally, treatment with recombinant human growth hormone should be considered in patients lacking catch-up growth within the first year after transplantation.

Keywords CKD-MBD · Renal transplantation · Children · Growth · Calcification · Parathyroid hormone · FGF23

Introduction

Mineral and bone disorders (MBD) are a major cause of morbidity in pediatric kidney transplant recipients and include growth failure, bone pain, fractures, and ectopic (vascular) calcification [1–4]. Complications in chronic kidney disease-associated MBD (CKD-MBD) are frequently observed after kidney transplantation (KTx), even with completely restored kidney function and are given in Table 1. Children suffering from end-stage CKD (ESKD) may already present with considerable complications in CKD-MBD at the time of KTx. Thus, the degree of preexisting renal osteodystrophy and cardiovascular changes are a major contributing factor to CKD-MBD after KTx. This is especially of importance in patients suffering from metabolic bone disease due to primary diseases such as nephropathic cystinosis [5]. Several other risk factors have also been identified, including immunosuppression (steroids, calcineurin inhibitors), alterations in the parathyroid hormone (PTH)—vitamin D—fibroblast growth factor 23 (FGF23) axis, changes in mineral metabolism (hypophosphatemia, hypomagnesemia), acidosis, unhealthy diet, reduced physical activity, muscle deficits, and impaired graft function [3, 4]. Kidney transplantation may correct some of the underlying risk factors for CKD-MBD, e.g., secondary hyperparathyroidism (SHPT), but may also introduce new ones, e.g., glucocorticoid-induced growth suppression. Thus, optimum management of these risk factors is crucial for children facing a lifetime with CKD. This review summarizes recent advances in the understanding of the pathophysiology, prevention, and treatment of CKD-MBD post KTx in children.

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Table 1 Common complications of CKD-MBD in pediatric transplant recipients

• Skeletal deformities, e.g., genu valgus and genu varum
•Bone pain
•Fractures
•Osteonecrosis
•Osteoporosis
•Impaired bone mineralization
•Short stature
•Ectopic (vascular) calcification
•Arterial stiffness
•Increased carotid intima media thickness
•Left ventricular hypertrophy and dysfunction

Pathophysiology

Preexisting mineral metabolism alterations

Children undergoing renal transplantation may already present with severe mineral metabolism alterations. In early CKD, high circulating FGF23 is the earliest detectable abnormality of mineral metabolism [6, 7]. FGF23 plasma concentrations start to rise as early as CKD stage 2, most likely due to an elevated phosphate load, in order to keep serum phosphate levels within the normal range by decreasing renal phosphate reabsorption and inhibiting renal synthesis of active vitamin D (calcitriol), which in turn reduces phosphate reabsorption from the gut. In addition, low levels of Klotho—the co-receptor for FGF23—may partially induce FGF23 resistance, resulting in a compensatory increase in FGF23 serum levels to maintain phosphate homeostasis. However, as renal function further declines, calcitriol deficiency results in hypocalcemia which, together with an increasing phosphate load, stimulates the synthesis of PTH by the parathyroid gland [6]. Increased PTH stimulates phosphaturia, renal 1α hydroxylase, and calcium resorption from the bone [8]. Elevated PTH levels are present in about 50% of pediatric CKD patients with an estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73 m^2 [7]. This allows the body to counterbalance the calcitriol deficiency-induced hypocalcemia and to keep serum phosphate levels within the normal range, despite advanced CKD, until the system decompensates and severe complications of CKD-MBD occur, i.e., renal osteodystrophy including bone pain, fractures, rickets, leg deformity, and growth failure, as well as ectopic (vascular) calcification and left ventricular hypertrophy [2, 6, 8]. Severe SHPT is associated with high bone turnover, ectopic calcification, anemia, left ventricular hypertrophy, and increased mortality in CKD patients [9–15]. Unfortunately, dialysis cannot reverse changes in CKD-MBD in children with ESKD and complications such as renal osteodystrophy and cardiovascular changes will progress in the majority of patients [16]. Indeed, high bone turnover, impaired bone mineralization, short stature, coronary artery calcifications, and left ventricular hypertrophy are noted in approximately 57%, 48%, 39%, 92%, and 48% of pediatric patients undergoing long-term dialysis, respectively [9, 10, 13, 17].

Changes in mineral metabolism after transplantation

The hypothetical course of circulating phosphate, PTH, and FGF23 in a patient undergoing KTx is illustrated in Fig. 1 [18]. This graph was originally based on data obtained in adult renal allograft recipients, but has also been recently confirmed in children [19]. Before KTx, the circulating levels of all three parameters increase in parallel with decreasing renal function. At the time of KTx, patients may present with excessively high levels of FGF23 and PTH. After KTx (recovery period), FGF23 and PTH may remain elevated for several months despite restored renal function. Both elevated PTH and FGF23 may contribute to the development of post-transplantation hypophosphatemia which has been noted in up to 10% of pediatric patients [19]. After the recovery period, all parameters may return to the normal range, although PTH can remain high in the case of tertiary hyperparathyroidism. In the long-term, graft function may be impaired resulting in reduced GFR and all three parameters may begin to increase again in the same order as in the pre-transplant period, i.e., starting with FGF23, followed by elevated PTH. Thus, patients with impaired graft function are prone to progressive CKD-MBD.

Although PTH levels usually decline in the majority of patients undergoing KTx, persistent SHPT after 12 months has been observed in 10–60% of patients [20, 21]. This was especially noted in cases of severe SHPT or tertiary hyperparathyroidism prior to KTx. Pre-transplant elevation of FGF23 is the strongest predictor of post-transplant elevation of FGF23 in children, and FGF23 levels independently predict hypophosphatemia and low 1,25-dihydroxyvitamin D levels [19]. Both may result in decreased osteoblast activity and progressive bone demineralization [3, 19]. In addition, low levels of 25-hydroxyvitamin D (25(OH)D) were noted in 50% of pediatric KTx patients and are associated with short stature and hypertension [22].

Hypomagnesemia

Hypomagnesemia has been shown to occur in approximately 40% of children after renal transplantation and is most likely due to magnesium wasting, secondary to the use of calcineurin inhibitors (CNI) [23, 24]. Magnesium deficiency may contribute to the development of osteoporosis as it is an integral component of the hydroxyapatite structure in the bone. It may also impair the magnesium-dependent hydrogen-

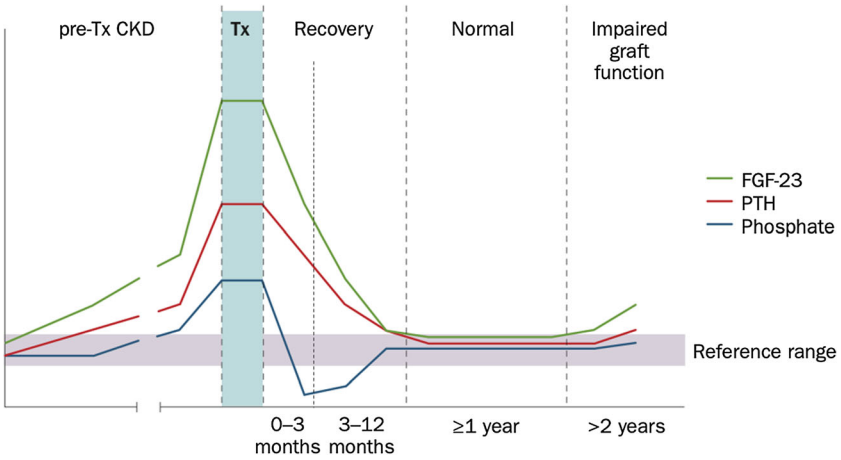

Fig. 1 Graphical overview of the hypothetical course of serum phosphate, parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23) levels in patients with CKD undergoing kidney transplantation (KTx). Before KTx, the circulating levels of all three parameters increase in parallel with the renal function decline. At the time of KTx, patients may have excessively high levels of FGF23 and PTH. After KTx (recovery period), FGF23 and PTH levels can remain high for months, despite restored renal function; this effect may contribute to the development of post-transplantation hypophosphatemia. After the recovery period, all parameters may return to the normal range, although PTH can remain high in the case of tertiary hyperparathyroidism. With impaired graft function, levels of all three parameters can increase again, starting with FGF23, as observed in the pre-transplantation CKD setting. CKD, chronic kidney disease. Figure reproduced with permission from Baia et al. [18].

potassium ATPase pump in bone cells, resulting in decreased pH of the extracellular matrix and, consequently, enhanced bone demineralization. In addition, magnesium deficiency is shown to impair PTH secretion and contribute to PTH resistance in target tissues in CKD patients [25]. In adult renal transplant recipients, hypomagnesemia is significantly associated with persistent SHPT 5 years after transplantation [26]. Hypomagnesemia has been associated with the development of new-onset diabetes after KTx and with decreased bone mineral content and low bone mineral density in malnourished children [27, 28]. Similarly, magnesium supplementation improved bone mineral content in healthy girls with a low dietary magnesium intake (< 220 mg/day) compared with controls [29].

Metabolic acidosis

Metabolic acidosis (serum bicarbonate < 22 mEq/L) is present in about 30% of pediatric transplant recipients and usually occurs when GFR is below 50% of norm, although nutritional intake (protein and acid load), catabolism, and alterations in electrolyte balance contribute to its development [30]. Subsequent metabolic and endocrine aberrations are triggered by metabolic acidosis and aggravate uremic growth failure. In fact, metabolic acidosis is significantly associated with decreased height gain and increased protein breakdown in children with CKD prior to and after KTx [31, 32]. Studies on metabolic acidosis in uremic animals have revealed a complex pattern of interrelated pathophysiological reactions [33]. Metabolic acidosis increases glucocorticoid production and protein degradation while concomitantly suppressing spontaneous pituitary growth hormone (GH) secretion and decreasing expression of the growth hormone (GH) receptor and insulin-like growth factor-I (IGF-I) receptor and decreasing IGF-I serum concentrations; these effects highlight the necessity for adequate control of metabolic acidosis in children with CKD [34, 35].

Immunosuppression

Glucocorticoids have a major impact on bone health. They are known to decrease bone formation, increase bone resorption, decrease calcium absorption, increase calcium wasting, decrease vitamin D, and increase PTH. In addition, they are known to impair gonadal function, and IGF-I synthesis [36–39]. A recent study in rodents showed that glucocorticoid treatment may impair bone growth via upregulation of FGF23 and FGF receptor 3 expression [40]. In line with this, pediatric KTx patients showed lower FGF23 serum levels after steroid withdrawal compared with controls kept on chronic treatment [40]. All of the aforementioned effects may contribute to impaired linear growth, osteonecrosis, fractures, and persistent deficits in cortical thickness, which are frequently noted in pediatric KTx patients on long-term glucocorticoid treatment [41].

Calcineurin inhibitors, such as cyclosporine A and tacrolimus, are known to inhibit synthesis of the vitamin D receptor and osteoprotegerin and to cause high-turnover osteoporosis [42]. In addition, they were shown to be associated with hypomagnesemia and increased PTH levels in adult KTx patients. However, their impact on bone health in pediatric renal transplant recipients remains to be clarified.

Experimental data shows evidence that treatment with mammalian target of Rapamycin (mTOR) inhibitors, including everolimus and sirolimus, negatively impacts osteoblast differentiation and growth plate structure and function [43, 44]. Treatment with sirolimus resulted in impaired linear growth and altered vascular invasion in the growth plate when given to young rats [43]. However, in case-control studies, similar growth rates were noted in transplanted children with and without mTOR inhibitor treatment [45, 46]. There is no evidence that treatment with mycophenolate mofetil or azathioprine impairs bone health.

Bone health and cardiovascular morbidity after transplantation

Bone deformities and fractures

Studies on long-term follow-up in pediatric KTx patients surviving into adulthood demonstrate a high burden of skeletal morbidity. Bartosh et al. showed a 41% prevalence of bone-joint abnormalities including genu varum an valgum, and a 23% prevalence of fractures [47]. Groothoff et al. also reported bone disease in 35% of patients, including disabling bone disorders (17.3%) and aseptic bone necrosis (11.8%) [48]. A markedly increased rate of vertebral fractures, as well as scoliosis, back pain, and disc degeneration, was noted in children after solid organ transplantation—the majority of whom received renal transplants [49, 50]. In the most recent study, a 10% prevalence of fractures was noted in children treated with concomitant glucocorticoid within the first 6 months post KTx [41]. Thus, despite a substantial improvement over the last 2 decades, transplanted children still suffer a high burden with CKD-MBD-associated complications.

Bone histomorphometry

Almost 100% of adult KTx patients show histological evidence of renal osteodystrophy [51, 52]. The most common manifestation is low bone turnover, which has been reported in up to 50% of patients. High bone turnover is associated with SHPT and observed in about 25–50% of adult KTx patients. By contrast, impaired mineralization is rarely observed (< 5%). Most studies in adults report a decline in bone formation and mineralization in the late post-transplant period [51–55]. A recent prospective study in adult patients undergoing bone biopsy while on dialysis and 2 years after KTx, or 2 years after baseline if KTx was not performed, showed a similar decrease in bone turnover over time in both groups [56].

Bone histology is rarely performed in pediatric KTx patients due to its invasiveness and cost. In a cross-sectional study, 10% of pediatric renal allograft recipients presented with adynamic bone disease and 23% of patients with high bone turnover [57]. The finding of persistent renal osteodystrophy in about 30% of patients, despite successful transplantation, is probably due to preexisting severe CKD-MBD related to long-term dialysis, persistent SHPT, the use of glucocorticoids, and/or vitamin D deficiency.

Bone mineral density and cortical structure

Bone mineral density (BMD) assessed by the two-dimensional technique dual-energy X-ray absorption appears to be normal in pediatric KTx patients when data is corrected for the degree of growth retardation [58]. Peripheral quantitative computed tomography (pQCT) is a three-dimensional technique which allows differentiation between trabecular and cortical bone. In addition, it measures volumetric BMD and bone dimensions [59]. In three cross-sectional studies, height-adjusted cortical thickness was found to be reduced in pediatric KTx patients when compared with controls [60–62]. In a prospective study, a reduced mean section modulus, which is a measure for bone strength, and a reduced muscle mass was noted in pediatric patients at the time of KTx compared with controls [41]. By contrast, trabecular BMD was significantly increased compared with controls in children aged below 13 years. Since SHPT results in the transformation of metaphyseal spongiosa, this finding is most likely due to PTH effects on the metaphysis. After KTx, cortical thickness improved significantly in this patient cohort. However, the section modulus did not improve within 12 months post-KTx, indicating persistent impaired bone strength in the patients despite marked improvement of SHPT and excellent graft function in the majority of patients. This may explain, at least partly, the high frequency of bone fractures (10% within 6 months post KTx) in this study. The persistent cortical deficits in pediatric KTx patients in the above-mentioned studies are most likely due to concomitant glucocorticoid treatment. However, pQCT data in transplanted children with complete steroid avoidance, or after steroid withdrawal, is lacking.

Growth

Although many of the metabolic and endocrine disorders contributing to uremic growth failure are resolved by renal transplantation, post-transplant catch-up growth is usually restricted to young children and occurs far from regularly [30, 47, 48, 63]. Persistent short stature is reported in about half of pediatric kidney transplant recipients. Beyond transplant function, age and extent of stunting at the time of KTx and glucocorticoid dosage is inversely associated with longitudinal growth.

Cardiovascular morbidity

Although KTx improves survival, subclinical cardiovascular organ damage is frequently noted in pediatric KTx patients, including left ventricular hypertrophy (43%), arterial stiffness (22%), atherosclerosis (58%), and endothelial dysfunction (77%) [64, 65]. Several risk factors have been shown to be associated with cardiovascular organ damage in these patients, e.g., hypertension, low eGFR, elevated body mass index, and treatment with mTOR inhibitors and glucocorticoids [64, 65]. It is important to note that the progression of vascular organ damage (aortal pulse wave velocity, carotid intima-media thickness) is significantly prevented by preemptive KTx when compared with initiating dialysis in children with ESKD [66]. By contrast, changes in left ventricular mass index were strongly associated with increased blood pressure but not with the mode of renal replacement therapy (dialysis or preemptive KTx). This highlights the need for stringent blood pressure control in KTx patients.

Coronary artery calcification is noted in 17–92% of children and young adults with childhood-onset ESKD [16]. Its presence is significantly associated with age, dialysis duration, serum phosphate, calcium, PTH, and c-reactive protein levels. Renal transplantation slows the rate of coronary artery calcification in patients with ESKD, but despite largely normalized serum calcium, phosphate, and PTH levels, they usually do not regress, at least in adults [67, 68].

Evaluation

As for every pediatric CKD patient, an anamnesis should be taken, including bone pain and walking difficulties, together with a thorough clinical assessment, including height, weight, signs of rickets or leg bowing, and calculation of annual height velocity, which should be done at regular intervals (Table 2) [69]. Young children and those who presented previously with clinical signs of CKD-MBD or impaired graft function should be seen more often. There is no evidence for performing regular X-rays in pediatric KTx patients. However, an X-ray of the left wrist should be considered in cases of persistent bone pain or SHPT to detect signs of demineralization and rickets and to establish growth potential (open epiphysis) in patients who are candidates for treatment with recombinant human GH (rhGH). In addition, calcium, phosphate, magnesium, alkaline phosphatase (ALP), PTH, and 25(OH)D levels should be regularly monitored [1, 70, 71]. The regular follow-up intervals as recommended by KDIGO are given in Table 3. These parameters should be considered together, with particular attention to trends in values [71]. Unfortunately, the above-mentioned biochemical parameters are poor predictors of bone disease, e.g., presence of impaired mineralization and high or low turnover. Therefore, KDIGO recommends assessment of bone histomorphometry, if the type of renal osteodystrophy will impact treatment decisions. However, this is rarely the case in transplanted children and may be considered in patients with unexplained fractures, especially when anticipating an underlying metabolic bone disease due to nephropathic cystinosis or primary hyperoxaluria. In adult KTx patients with an eGFR > 30 mL/min/1.73m^2, KDIGO suggests using BMD to assess whether fracture risk results will alter therapy. As mentioned above, BMD values are normal in pediatric KTx patients when normalized to height and data on the predictive value of BMD measurements in assessing fracture risk in these patients is lacking. Therefore, there is currently no evidence for its clinical use in this population. The same holds true for newer techniques such as high-resolution pQCT or MRI.

Treatment options

In general, a lifestyle including a healthy diet, regular physical activity (a minimum of 30 min on most days of the week), and

Table 2 Recommended frequency of assessment (in months) of length/height, skeletal status, and length/height velocity by CKD stage and age

CKD stage				
	1–2T	3T	4T	4–5T
Length/height/skeletal status*				
Age 0–1 years	1–2	0.5–2	0.5–2	0.5–2
Age 1–3 years	2–3	1–3	1–2	1–2
Age > 3 years	3–6	3–6	1–3	1–3
Length/height velocity				
Age 0–1 years	1–2	0.5–2	0.5–2	0.5–2
Age 1–3 years	3–6	1–6	1–3	1–3
Age > 3 years	6	6	6	6

Table adapted from [69], reproduced with permission; *History of pain and signs of rickets and leg bowing

Table 3 Follow-up of biochemical parameters of CKD-MBD after kidney transplantation

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

CKD, chronic kidney disease; Table adapted from KDIGO [70], reproduced with permission

not smoking is recommended, as for other CKD patients. Patients should be provided with an adequate dietary calcium and phosphate intake (at least 100% of daily recommended intake in healthy children) to allow for bone mineralization and growth [1, 69]. Patients should avoid foods high in salt as high sodium intake promotes hypertension and hypercalciuria [72]. The latter may impair bone formation. In addition, a high intake of cola drinks should be avoided as this has been linked to decreased BMD and increased fracture risk in the general pediatric population and delays bone healing in rodents [73].

Correction of alterations of vitamin D and mineral metabolism

KDIGO recommends that treatment choices be influenced by the presence of CKD-MBD, as indicated by abnormal levels of calcium, phosphate, PTH, ALP, and 25(OH)D [1, 70]. It is important to note that these parameters should be considered together with particular attention to trends in values. KDIGO also recommends considering treatment with vitamin D analogs or bisphosphonates to treat bone disease in adult patients with an eGFR above 30 mL/min/1.73 m^2 during the first 12 months after KTx. However, there is no evidence to recommend treatment with bisphosphonates in kidney-transplanted children.

We suggest evaluation of vitamin D deficiency as the first step, as it is present in approximately 50% of pediatric KTx patients and may promote hypophosphatemia and SHPT [22]. Oral vitamin D supplementation with cholecalciferol or ergocalciferol was recommended in vitamin D-deficient KTx patients aiming at 25(OH)D target levels of 75–12 nmol/L (30–50 ng/mL) as in CKD patients prior to transplantation [69, 74]. In the second step, treatment with active vitamin D should be considered, in the presence of PTH levels above the target range, based on the stage of CKD, if vitamin D deficiency is absent or corrected [1]. We suggest applying the minimum PTH-suppressive dosages as recommended for CKD patients prior to KTx [75]. It is important to note that there is no agreement on the optimum PTH target range and consequently recommended CKD-stage-dependent PTH target range values differ widely [69, 76–79]. However, most important is the acknowledgment that none of these recommendations have been validated in a large pediatric CKD cohort study/investigation, especially in children after renal transplantation. Parathyroidectomy should be considered in patients with persistent severe, therapy-refractory SHPT, i.e., with radiological indications and hypercalcemia [78].

In patients showing persistent post-transplant hypophosphatemia, a high phosphate diet and initiation of oral phosphate supplementation is recommended in order to reach low normal levels (for age). However, phosphate supplementation may stimulate both PTH and FGF23 levels, which may further stimulate renal phosphate wasting, causing a vicious circle. Therefore, the lowest possible phosphate dosages should be applied in these patients.

Magnesium deficiency is known to promote osteoporosis and PTH resistance, and it should be corrected with oral magnesium supplementation aiming at levels above the lower normal limit.

Correction of acidosis

Metabolic acidosis should be corrected by oral bicarbonate, aiming for bicarbonate levels above 22 mEq/L, as recommended in other CKD patients [69]. However, this may not be possible in all patients because high doses of sodium bicarbonate may promote hypertension.

Steroid avoidance

A meta-analysis of 5 randomized clinical trials (RCTs) on growth outcome using steroid minimization protocols in pediatric KTx patients showed a significant improvement in height *z* scores in the steroid-avoidance group, particularly within the first year after steroid withdrawal and in prepubertal patients [80]. Therefore, it is recommended to minimize or completely avoid glucocorticoid use in children who have growth potential, if possible.

Growth hormone treatment

Several RCTs have shown the benefit of rhGH therapy in short pediatric KTx patients. A meta-analysis of 5 RCTs demonstrated that patients receiving rhGH therapy had a significantly higher height velocity 1 year after initiation of therapy than the control group, with a mean difference in height z score of 0.68 (95% CI 0.25–1.11) [81]. In addition, treatment with rhGH resulted in increased osteoblast activity, bone formation, and turnover in short pediatric KTx patients [82]. Consequently, a recent European guideline recommends initiating rhGH therapy 1 year after transplantation if spontaneous catch-up growth does not occur—defined as a height below the third percentile for age and sex and a growth velocity below the twenty-fifth percentile—and steroid-free immunosuppression is not a feasible option. The latter may be the case in patients with a high immunological risk, particularly in children with suboptimal graft function (eGFR < 50 mL/min/1.73 m^2) [83]. Growth hormone should be given at a dose of 0.045–0.05 mg/kg body weight per day by subcutaneous injection in the evening and parents and physicians may encourage children from about 8–10 years of age to do the rhGH injections on their own, if adequate training and adherence is ensured. Clinical visits every 3–6 months are recommended to monitor height, growth velocity, pubertal development, skeletal maturation on wrist radiography, renal function, thyroid hormone levels, and serum glucose levels. If growth velocity in the first year of rhGH treatment is less than 2 cm per year over baseline, then assessment of patient adherence to rhGH therapy, including measurement of serum IGF-I levels and weight-adjusted rhGH dosage, is recommended. Finally, rhGH should be stopped when epiphyseal closure is confirmed [83].

Key summary points

- Monitoring of CKD-MBD in pediatric kidney transplant recipients should primarily focus on assessment of growth, leg deformities, and serum levels of calcium, phosphate, magnesium, bicarbonate, alkaline phosphatase, 25(OH)D, and PTH.
- Regular physical activity, healthy diet, and preservation of transplant function are recommended.
- Steroid-sparing immunosuppressive protocols and adequate treatment of alterations in vitamin D, phosphate, alkaline phosphatase, calcium, and PTH as well as correction of metabolic acidosis are recommended.
- Treatment with active vitamin D is recommended in case of persistent secondary hyperparathyroidism, using the minimum PTH-suppressive dosages and aiming for the recommended CKD stage-dependent PTH target range.
- Treatment with recombinant human growth hormone should be considered in patients lacking catch-up growth within the first year after renal transplantation.

Multiple choice questions

1. What is a typical clinical feature of post-transplant CKD-MBD?
   a. Bone pain
   b. Delayed sexual maturation
   c. Increased bone mineral density
   d. Low bone turnover
2. Post-transplant CKD-MBD is often due to
   a. Mycophenolate mofetil treatment
   b. Decreased FGF23 levels
   c. Glucocorticoid treatment
   d. Preemptive renal transplantation
3. Management of post-transplant CKD-MBD does focus on
   a. Maintenance of regular physical activity
   b. High sodium intake
   c. High dose treatment with active vitamin D
   d. Treatment with bisphosphonates
4. Treatment with recombinant human growth hormone should be considered
   a. Within 12 months post transplantation
   b. If height velocity is below the 30th percentile for age and gender
   c. If eGFR is above 50 mL/min/1.73 m^2
   d. If height is below the 3rd percentile for age and gender
   e. In case of concomitant glucocorticoid therapy
5. Which statement regarding control of PTH levels is right?
   a. Correction of vitamin D deficiency should be done before starting active vitamin D
   b. Active vitamin D should be started within the first three months after transplantation
   c. Hypercalcemia stimulates PTH levels
   d. PTH levels should be above 2 times the upper limit of normal

Compliance with ethical standards

Conflict of interest D.H. has received research grants from Sandoz, Kyowa Kirin, Horizon, and Amgen and has received speaker and/or consultant fees from Amgen, Sandoz, Kyowa Kirn, Pfizer, Merck Serono, Horizon, and Chiesi. M.L.N. received travel grants from Amgen.

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Answers to multiple choice questions:

1. a; 2. c; 3. a; 4. d; 5. a