The management of mineral and bone disease after kidney transplantation: A narrative overview

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Abstract

Post-transplant mineral bone disease (PT-MBD) is associated with increased morbidity and mortality in kidney transplant recipients. Bone abnormalities can range from adynamic bone disease to severe persistent hyperparathyroidism with associated hypercalcemia and hypophosphataemia. In addition, these patients can develop other complications such as osteopenia and osteoporosis; further increasing the risk of fragility fractures. Appropriate management is challenging, given the lack of robust evidence. Bone turnover biomarkers and imaging studies are not entirely validated to differentiate between these pathological entities. Available interventions to control high turnover bone disease include calcimimetic drugs (Cinacalcet) and surgical parathyroidectomy. Cinacalcet has been shown to improve bone biochemistry and reduce the number of required parathyroidectomies. However, none of the meta-analyses identified a significant reduction in the overall mortality. Cinacalcet remains the treatment of choice for high turnover bone disease in the first year after transplantation, sometimes serving as a precursor to the surgery. In general, severe hyperparathyroidism does not respond adequately to cinacalcet alone, and many of these patients would eventually require parathyroidectomy. In our opinion, total parathyroidectomy should be avoided as this leads to undetectable PTH and subsequent adynamic bone disease. Anti-resorptive treatment, on the other hand, is indicated for proven osteoporosis if excretory graft function permits. In this narrative review, we provide an overview of the management of PT-MBD, based on the current best available evidence.

Introduction

Kidney transplantation remains the best treatment option for most patients with end-stage kidney disease (ESKD) as it confers superior survival, less cardiovascular risk and better quality of life [1-4]. Moreover, transplantation restores both endocrine and exocrine kidney function, which is essential for the amelioration of the established bone disease. Yet, transplanted patients carry substantial risk of fractures, morbidity and mortality related to post-transplant mineral bone disease (PT-MBD) [5-7]. This happens especially in patients who have long been waiting for a kidney transplant Persistent hyperparathyroidism is observed in 17% to 50% of transplant recipients in their first year after transplantation [8-10]. In addition, immunosuppression plays an important role in the progression of PT-MBD [11]. In this review, we discuss current therapeutic options in the management of PT-MBD.

Discussion

Post-transplant mineral bone disease (PT-MBD)

Mineral bone disease associated with pre-existing chronic kidney disease (CKD-MBD); immunosuppressive agents and; the glomerular filtration rate (GFR) achieved after transplantation are the three main factors which affect the progression of PT-MBD. CKD-MBD is a multi-system disorder characterized by a number of overlapping conditions involving the (a) skeletal system with defects in bone turnover and mineralization (b) bone biochemistry with abnormal parathyroid hormone (PTH) levels, fibroblast growth factor-23 (FGF-23) and vitamin D metabolism, and (c) extra-skeletal involvement including soft tissue and vascular calcification [12,13]. At one end of the spectrum is a low turnover state causing adynamic bone disease, while osteitis fibrosa represents the other end with a high turnover state [14,15]. The difficulty of PT-MBD management is partly attributed to the lack of robust evidence and the lack of reliable and non-invasive tools for investigation. Bone turnover biomarkers (PTH, bone-specific alkaline phosphatase and osteocalcin) are not sufficiently sensitive or specific to detect abnormalities in bone composition and function [5,16]. Moreover, the currently available imaging modalities have not been thoroughly validated to distinguish between these interplaying bone conditions. It has been only recently that the Kidney Disease Improving Global Outcomes (KDIGO) 2017 guidelines [13] suggested the use of bone mineral density measurements using dual-energy X-ray absorptiometry (DEXA) to assess fracture risk in the CKD and dialysis population as new prospective studies became available. These guidelines also suggest a bone biopsy to be performed in the CKD and post-transplant population (within the first year) if this is considered to impact treatment decisions, although this statement is not graded due to lack of evidence. There are insufficient data to guide therapy after the first year of transplantation [12,13]. In our experience, routine

post-transplant bone biopsies are only performed in a few centres of excellence; many centres lack the expertise to interpret bone histology. Also, very few studies identify bone biopsy histology as one of the primary outcome measures, and the local bone histology is not always representative of the entire skeleton.

Renal Hyperparathyroidism

CKD related hyperparathyroidism can be broadly subdivided into secondary and tertiary hyperparathyroidism. Secondary hyperparathyroidism is regarded as a physiological response to hypocalcaemia and hyperphosphatemia, which result from activated vitamin D (1,25-dihydroxycholecalciferol) deficiency, and increased FGF-23, associated with CKD [17,18]. Prolonged secondary hyperparathyroidism can eventually lead to tertiary hyperparathyroidism, characterized by autonomous production of PTH, resulting in increased bone turnover, bone demineralization, disturbed bone structures and, subsequent effects of hypercalcemia and hyperphosphatemia [17,19]. Some studies suggest that around 20% of patients may have associated parathyroid adenomas [19,20]. Post-transplant hyperparathyroidism is associated with defective bone mineralization, increased fracture risk, worse graft function, cardiovascular morbidity and higher all-cause mortality [8,9,21,22]. Between 50% and 85% of the patients receiving a kidney transplant develop significant hypophosphatemia in the first-year post-transplant; a manifestation related to the persistent hyperparathyroidism and FGF-23 related renal phosphate wasting [23-25]. In normal physiology, most of the filtered phosphate is reabsorbed at the proximal convoluted tubule. It is thought that FGF-23 is responsible for the inhibition of renal phosphate re-absorption via the co-receptor Klotho, which is abundantly expressed in the renal tissue [26,27]. Therefore, high level of FGF-23 present in the immediate post-transplant period leads to profound phosphate wasting through the newly acquired glomerular mass. Elevated FGF-23 has been identified as an independent risk factor for mortality and graft loss in kidney transplant recipients [28].

The occurrence of post-transplant hypercalcemia has been reported in 12% to 66% of patients, primarily related to persistent hyperparathyroidism [29-32]. The incidence of hypercalcemia seems to peak in the first 3 months after transplantation [29,33]. Persistent hypercalcemia has been associated with the development of microcalcifications in the transplanted kidney, leading to transplant dysfunction and premature failure [33-35].

Standard medical therapy

Standard medical therapy in the CKD and dialysis population includes phosphate dietary restriction, phosphate binders, native vitamin D supplementation and vitamin D analogue treatment to suppress PTH secretion and ameliorate bone biochemistry, as recommended by various international guidelines [12,13,36-38]. Interestingly, there is no clear definition and explicit recommendations on the optimal targets of 25-hydroxycholecalciferol in the post-transplant period [39]. The KDIGO 2017 update is very clear that clinical decisions should not be based on solitary PTH values, but on 'persistently' and/or 'progressively' elevated levels [13]. Also, the use of calcitriol and vitamin D analogues should be reserved for patients with severe and progressive hyperparathyroidism [13]. Transplanted patients with low bone mineral density and estimated GFR greater than 30 ml/min/1.73m^2 might benefit from vitamin D metabolites and/or antiresorptive therapies [13].

Cinacalcet

Cinacalcet enhances the sensitivity of the calcium-sensing receptor of the parathyroid gland to extracellular calcium, thereby suppressing PTH secretion, leading to a reduction in serum calcium [40,41]. The KDIGO guidelines suggest that calcimimetics, calcitriol, or vitamin D analogues alone or in combination, can be used for patients on dialysis requiring PTH-lowering therapy (grade 2B recommendation) [12,13]. Vitamin D metabolites should be reduced or stopped in patients with hyperphosphatemia and hypercalcemia, while cinacalcet should be reduced or stopped in patients with hypocalcemia [12].

In the CKD and dialysis population, the use of cinacalcet has shown a reduction in parathyroidectomy [42-44], reduction in fracture risk [42,44], reduction in cardiovascular-related hospitalization [44] and increased rate of achieving the KDOQI targets for PTH [45] (Table 1). However, data on the use of cinacalcet in the transplant population is quite limited as kidney transplant recipients were frequently excluded. The meta-analysis conducted by Cohen, et al. [46], composed entirely of non-randomised studies, showed a PTH reduction of 102 pg/mL (95% confidence interval: -69 to -134). None of the meta-analyses involving cinacalcet identified a significant decrease in mortality.

The severity of hyperparathyroidism at which cinacalcet is preferred to parathyroidectomy remains poorly defined as many studies lacked precision in the reporting of PTH levels (e.g. simply defined as ≥ 300 pg/mL) [47,48]. Arenas and colleagues [49] reported a mean PTH reduction of almost 70%, from an initial level of 826 ± 325 pg/mL to 561 ± 367.3 pg/mL and 248.1 ± 77.3 pg/mL at 5 and 9 months respectively. It seems that patients with higher PTH levels are more resistant to cinacalcet treatment. Indeed, merely 22% of patients achieved a PTH ≤ 300 pg/mL when the pre-treatment level exceeded 800 pg/mL [50]. Furthermore, the use of cinacalcet is frequently limited by adverse events (Table 1) and many patients tend to receive inadequate dosing for effective PTH inhibition. Compared to parathyroidectomy, the PTH levels tend to return to baseline immediately once cinacalcet is discontinued. Abrupt peri-transplant withdrawal of cinacalcet in patients receiving doses above 60 mg/day was associated with hypercalcemia and hypophosphatemia [51]. For this reason, we believe that patients on cinacalcet before transplantation should be maintained on the same regimen in the peri-operative period to avoid rebounds in the PTH levels and other biochemical abnormalities.

Parathyroidectomy

Parathyroidectomy is considered by many as the definitive therapy for significant hyperparathyroidism, particularly in prospective kidney transplant recipients. In general, parathyroidectomy in the CKD and dialysis patients achieves sustained PTH reductions, although recurrence is still possible, especially with partial parathyroidectomy [52-55]. There is sparse evidence comparing the effects of cinacalcet to parathyroidectomy in the post-transplant period. In a small randomised control trial (N=30) conducted by Cruzado and colleagues [56], subtotal parathyroidectomy resulted superior to calcimimetics in achieving normocalcemia at 12 months, and more cost-effective if cinacalcet was used for more than 14 months. A recent retrospective analysis involving kidney transplant recipients, who underwent parathyroidectomy or administered cinacalcet for tertiary hyperparathyroidism, cinacalcet was effective to achieve normocalcemia but was not effective in achieving normal PTH levels compared to parathyroidectomy [10]. The KDIGO guidelines suggest that parathyroidectomy is a valid treatment option for patients with CKD 3–5D who suffer from severe hyperparathyroidism and who fail to respond to medical therapy (grade 2B recommendation)

Table 1. Summary of the meta-analyses investigating the use of cinacalcet for the treatment of hyperparathyroidism in the CKD and transplant population, looking at the primary outcomes and adverse events

Meta-analysis	Study population & sample size	Main outcomes	Adverse events
Sekercioglu, *et al.* [42]	CKD3-5 CKD5D 24/24 RCT N=8311	Reduction in parathyroidectomy: RR: 0.30, 95% CI: 0.22–0.42. Reduction in fracture risk: RR: 0.59, 95% CI: 0.13–2.60. No significant difference in all-cause mortality: RR: 0.96, 95% CI: 0.89–1.04.	Hypocalcemia: RR: 6.0, 95% CI: 3.65–9.87. Nausea: RR: 2.16, 95% CI 1.46–3.21. Vomiting: RR: 2.15, 95% CI 1.66–2.80.
Li, *et al.* [45]	CKD5D 6/6 RCT N=2548	Increased achievement of KDOQI target for PTH: RR: 3.51, 95% CI: 2.38–5.17. No data on parathyroidectomy and mortality rate reported.	Hypocalcemia: RR: 3.53, 95 % CI 1.72–7.22. Nausea: RR: 2.96, 95 % CI 1.53–5.70. Vomiting: RR: 2.21, 95% CI: 1.60–3.04. Diarrhoea: RR: 1.39, 95 % CI 1.00–1.92.
Palmer, *et al.* [43]	CKD5D 18/18 RCT N=7446	Reduction in parathyroidectomy: RR: 0.49, 95% CI: 0.40–0.59. No significant difference in all-cause mortality: RR: 0.97; 95% CI: 0.89–1.05.	Hypocalcemia: OR: 6.98, 95% CI: 5.10–9.53. Nausea: OR: 2.02, 95% CI: 1.45–2.81. Vomiting: OR: 1.97, 95% CI 1.73–2.24.
Zang, *et al.* [52]	CKD5D 15/15 RCT N=3387	Decreased in PTH levels: OR: 10.75, 95% CI: 6.65–17.37, *p*=0.001. No significant difference in all-cause mortality: OR: 0.86, 95% CI: 0.46–1.60.	Hypocalcemia: OR: 2.46, 95% CI: 1.58–3.82, p=0.001. Nausea: OR: 2.45, 95% CI: 1.29–4.66, p=0.006 Vomiting: OR: 2.78, 95% CI: 2.14–3.62, p=0.001. Diarrhoea: OR: 1.51, 95% CI: 1.04–2.20, p=0.030. Upper respiratory tract infection: OR: 1.79, 95% CI: 1.20–2.66, p=0.004.
Cunningham, *et al.* [44]	CKD5D 4/4 RCT N= 1184	Reduction in parathyroidectomy: RR: 0.07, 95% CI 0.01–0.55. Reduction in fracture risk: RR: 0.46, 95% CI: 0.22–0.95. Reduction in cardiovascular related hospitalisation: RR: 0.61, 95% CI: 0.43–0.86. No significant difference in all-cause mortality: RR 0.81, 95% CI 0.45–1.45.	Not reported.
Cohen, *et al.* [46]	Transplant 15/21: prospective 6/21: retrospective N=411	Reduction in PTH by 102 pg/mL 95% CI: -69 to -134. No significant change in creatinine. No data on parathyroidectomy and mortality rate reported.	Not reported.

RR: relative risk, OR: odds ratio, CI: confidence interval, PTH: parathyroid hormone

[12,13]. This has been endorsed by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative [36], Canadian Society of Nephrology [38] and European Best Practice Guidelines (ERPB) [37]. A registry analysis suggested a significant reduction in mortality following parathyroidectomy compared to matched patients receiving medical therapy alone [57]. Parathyroidectomy has been associated with a 31% reduction in the risk of fracture [58].

The next key question is the optimal timing of parathyroidectomy. Is parathyroidectomy best performed before transplantation? Or perhaps should we wait until after transplantation to allow sufficient time for potential spontaneous amelioration? Indeed, hyperparathyroidism may resolve entirely in the post-transplant period, particularly if patients are asymptomatic [8,9]. The ERBP suggest that parathyroidectomy should be considered as a last resort, particularly in the first 12-18 months post-transplant. Also, several retrospective studies indicated that post-transplant parathyroidectomy could be associated with a temporary decline in the transplant function [22,30,59-64]. We believe that waitlisted patients requiring parathyroidectomy should be ideally operated before transplantation. Should however a kidney offer become available before surgery, we prefer to postpone the parathyroidectomy rather than transplantation, but one should allow enough time for graft stabilization before proceeding to eventual parathyroidectomy.

The optimal surgical technique is also still an area of controversy. While total parathyroidectomy was advocated in the early days of parathyroid surgery [65-67], we know that this procedure is frequently associated with profound post-surgical hypocalcemia and subsequent adynamic bone disease due to over-suppressed PTH. In general, total parathyroidectomy with immediate auto-transplant or subtotal parathyroidectomy is the surgical procedure of choice. Nonetheless, there is very little evidence that total parathyroidectomy

with immediate auto-transplantation is superior or inferior to subtotal parathyroidectomy [12].

Immunosuppression

Although corticosteroid therapy is an essential component of modern immunosuppressive regimes, it is widely believed that their use contributes directly to the progression of PT-MBD [11,68]. Corticosteroids are responsible for increasing bone resorption and impairing bone formation leading to a net loss of bone volume and decreased turnover [69,70]. Even though corticosteroid avoidance strategies may seem attractive, two meta-analyses conducted by Knight, *et al.* [71] and Pascual, *et al.* [72] reported similar patient and allograft survival but a higher incidence of acute rejection in the corticosteroid withdrawal group. Indeed, patients developing acute rejection might be exposed to higher cumulative doses of corticosteroids administered as rescue pulses. The KDIGO guidelines published in 2009 [73] suggest that patients who have low immunological risk and who receive induction therapy may have early corticosteroid withdrawal in the first week after transplantation. We believe that early steroid withdrawal can be employed as a "trade-off" for increased risk of fragility fractures, particularly in patients who have a low immunological risk but high-risk of developing post-transplant osteoporosis. Calcineurin inhibitors (CNI) have also been implicated in the progression of bone resorption, albeit to a lesser degree [74]. Indeed, both CNIs and corticosteroids have been linked to the development of post-transplant osteoporosis [75]. Conversely, mycophenolate derivatives and azathioprine seem to have no apparent effect on bone metabolism, although evidence is quite sparse [76]. At present, there is no conclusive clinical data on the use of mammalian target of rapamycin inhibitors concerning the progression of PT-MBD [11].

Post-transplant osteoporosis

The KDIGO guidelines [12,13] suggest that transplant patients with GFR higher than approximately 30 ml/min/1.73m^2 who are diagnosed with osteoporosis within the first 1 year of transplantation can be treated with bisphosphonates or other antiresorptive medications. Most of the experience gained on the use of bisphosphonates in the post-transplant period comes from studying pamidronate, where most studies suggested successful prevention of bone loss [75]. The use of Denosumab (RANKL inhibition with anti-resorptive properties) also resulted in significant improvement of the bone mineral density in the lumbar spine, hip, tibia and radius in the first year after transplantation [77]. The increasing experience with the use of antiresorptive medications in patients with CKD may not justify withholding osteoporosis medications if a bone biopsy is not available [78]. However, in patients with lower GFRs, treatment strategies should take into consideration the underlying MBD, and a bone biopsy should be considered before initiating therapy [13]. In these patients, the use of bisphosphonates has been associated with exacerbation of any underlying adynamic bone disease, whereas Denosumab has been linked with significant hypocalcemia. Teriparatide (recombinant PTH) seems to be effective in treating osteoporosis in the context of adynamic bone disease, but its use remains mostly experimental [79-82].

Conclusion

PT-MBD is associated with increased morbidity and mortality in kidney transplant recipients. Pre-existing CKD-MBD remains the primary underlying driving mechanism, exacerbated with the use of immunosuppressive agents and the degree of post-transplant CKD. Evaluation and monitoring of post-transplant bone health using regular bone biochemistry, baseline DEXA scan and bone biopsy in high-risk patients is suggested for appropriate and timely management. Management of PT-MBD can be challenging, given the lack of robust evidence. Most of the evidence is currently being extrapolated from studies in the pre-transplant period. Cinacalcet has been shown to improve bone biochemistry and reduce the number of required parathyroidectomies. However, none of the meta-analyses identified a significant reduction in the overall mortality. It remains the treatment of choice for high turnover bone disease in the first year after transplantation, sometimes serving as a bridge to surgery. Nonetheless, severe hyperparathyroidism does not usually respond adequately to cinacalcet alone, and many of these patients would eventually require parathyroidectomy. Meanwhile, vitamin D analogues, phosphate binders and limiting corticosteroid exposure in selected patients are important measures to improve the outcome of PT-MBD, with anti-resorptive therapy being reserved for those with proven osteoporosis and high-risk for fractures. Finally, multicenter collaboration is urgently required to establish the optimal therapeutic strategies and validate models for predicting therapeutic response in PT-MBD.

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