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Management of mineral and bone disorders in renal transplant recipients

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Abstract

The management of post-transplantation bone disease is an increasingly complex problem that remains under-appreciated in clinical practice. In these patients, pre-existing metabolic bone disorder is further impacted by the use of immunosuppressive medications (glucocorticoids and calcineurin-inhibitors), variable post-transplantation renal allograft function, and post-transplantation diabetes mellitus. The treatment of post-transplantation bone loss should begin pre-transplantation. All patients active on transplant waiting lists should be screened for bone disease. Patients should also be encouraged to take preventative measures against osteoporosis such as regular weight-bearing exercise, smoking cessation and reducing alcohol consumption. Biochemical abnormalities of disordered mineral metabolism should be corrected prior to transplantation wherever possible, and because these abnormalities commonly persist, post transplant hypophosphatemia, persistent hyperparathyroidism and low vitamin D levels should be regularly monitored and treated. Bone loss is greatest in the first 6-12 months post-transplantation, and this is the period where any intervention is likely to be of greatest benefit. There is strong evidence that bisphosphonates prevent post-transplantation bone loss, however, data are lacking that this clearly extends to a reduction in fracture incidence. Denosumab is a potential alternative to VDRAs and bisphosphonates in reducing post-transplantation bone loss; however, further studies are needed to demonstrate its safety in patients with a significantly reduced eGFR. Clinical judgement remains the cornerstone of this complex clinical problem, providing a strong rationale for the formation of combined endocrinology and nephrology clinics to treat patients with CKD-MBD, before and after transplantation.

Introduction

The management of bone disease has often been neglected post-transplantation, when the clinical focus is on allograft function and immunological sequelae. However, most renal transplant recipients (RTRs) have pre-existing Chronic Kidney Disease - Mineral and Bone Disorder (CKD-MBD), which results in changes to mineral metabolism and reduced bone mineral density (BMD) and quality that are linked to an increased incidence of fractures and cardiovascular disease (CVD)[1]. Pre-existing renal osteodystrophy, including adynamic bone disease, is further impacted post-transplantation by the use of immunosuppressive medications (glucocorticoids and calcineurin-inhibitors), variable renal allograft function and post-transplantation diabetes mellitus[2].

Post-transplantation bone loss is greatest in the first 6-12 months, and the majority of post-transplantation fractures are peripheral. The incidence has been variably reported but exceeds 40% in some studies[3]. In a study comparing recent RTRs to dialysis patients on the transplant waiting list, the relative risk of fractures is 34% higher in the first 6 month post-transplantation[4]. The use of prednisolone is the main cause of bone loss, as highlighted by a longitudinal bone biopsy study performed early post-transplantation[5]. The main findings were a decrease in osteoblast number, early osteoblast apoptosis, a reduced bone formation rate and prolonged mineralisation lag time. Significantly, these findings were present in patients with both high and low bone turnover, suggesting that these findings are independent of pre-existing CKD-MBD. Long-term, a degree of recoupling between bone formation and resorption occurs, and depending on renal allograft function and abnormalities of mineral metabolism, BMD may stabilise or even improve post-transplantation[6].

Variable strategies and treatments are used to detect bone loss and preserve BMD after transplantation; however none have been shown to clearly alter fracture risk. We now discuss the 2009 KDIGO (Kidney Disease Improving Global Outcomes) guidelines for the management of bone disease in RTRs, and review recent evidence with a focus on implications for changes to clinical practice.

KDIGO guidelines

The current KDIGO guidelines for the care of kidney transplant recipients were published in 2009[7] and for topics relating to bone, were based on the KDIGO CKD-MBD guidelines published earlier that year[1]. The Australasian (KHA-CARI) adaptation of the KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients was published in 2012, but did not address the specific issue of bone disease post-transplantation[8].

Briefly, the 2009 KDIGO guidelines recommended that in the immediate post-kidney transplant period, serum calcium and phosphate be measured at least weekly until stable. (1B) and that 25-hydroxyvitamin D (25[OH]D) levels might be measured, with vitamin D deficiency and insufficiency corrected using treatment strategies recommended for the general population (2C). The guidelines suggested that in patients with an estimated glomerular filtration rate (eGFR) greater than approximately 30 mL/min/1.73 m^2, BMD be measured in the first 3 months after kidney transplantation if patients received corticosteroids or had general population risk factors for osteoporosis (2D), and if those patients were found to have a low BMD, treatment with vitamin D, calcitriol/alfacalcidol or bisphosphonates be considered (2D). It was suggested that treatment choices be influenced by levels of calcium, phosphate, parathyroid hormone (PTH), alkaline phosphatase (ALP) and 25(OH)D (2C), that it was reasonable to consider a bone biopsy to guide treatment, specifically before the use of bisphosphonates due to the high incidence of adynamic bone disease. (Not Graded) and that BMD testing not be performed routinely in CKD stages 4–5T, because it did not adequately predict fracture risk (2B)

Screening and diagnosis

Biochemical assessment

KDIGO guidelines recommend the measurement and calcium and phosphate at least weekly until levels normalise. PTH and serum 25(OH)D levels are also commonly measured, however, there is no recommendation or agreement as to the threshold level for intervention, or what constitutes an acceptable level. Bone specific ALP (BSAP) is seldom measured in Australia due to limited availability and cost, instead tissue non-specific ALP is commonly used as a surrogate marker. In non-CKD, bone turnover markers (BTM) are used for fracture prediction and assessment of treatment efficacy[9]. Pro-collagen type 1 N propeptide (P1NP) and C-terminal cross-linking telopeptide (CTX) have been selected for further standardisation[10], although these markers both accumulate in CKD where their interpretation may be problematic. However, a potential utility may be in RTRs with near-normal renal function. We believe that the use of BSAP has diagnostic potential in CKD cohorts, because bone formation rates, as assessed by histomorphometry, correlate better with BSAP compared with total ALP[11]. BSAP is also better at differentiating high and low turnover bone disease (when compared with PTH), and combined with PTH, improves the prediction of adynamic bone disease[12]. A recent study found that BSAP measured at regular intervals predicted all fracture types in patients with CKD stage 5D[13]. Intact PINP, which demonstrates hepatic metabolism, as well as tartrate resistant acid phosphatase 5b (TRAP5b) assays are also under investigation as BTMs in CKD.

Radiological and histological assessment

Dual-energy X-ray absorptiometry (DXA) is recommended for the diagnosis of osteoporosis in the general population, and the use of DXA in patients with CKD stages 1-3 should follow general population guidelines. The use of DXA in advanced stages of CKD remains challenging. BMD testing generally underestimates fracture risk in CKD, as patients commonly have underlying metabolic bone disease, which increases fracture risk independent of BMD. Also, DXA measurements cannot distinguish between cortical and trabecular bone (differentially affected in secondary hyperparathyroidism), and are confounded by concomitant vascular calcification. However a recent meta-analysis in pre-dialysis and dialysis CKD suggested that BMD can, in fact, discriminate fracture status in these cohorts[14]. This supports *post-hoc* analyses of large osteoporosis trials that suggest BMD measurements may be useful in CKD[15]. Newer techniques such as high-resolution peripheral quantitative computed tomography (HRpQCT) can quantify cortical and trabecular volumetric BMD and also estimate cortical BMD and porosity, however, currently these are limited to research applications. The routine use of bone biopsy in Australia is limited by a lack (in most hospitals) of expertise in obtaining, processing and analysis of bone biopsy samples. Its utility in confirming low turnover bone disease in RTRs remains invaluable, especially given the increased use of anti-resorptive therapies in this cohort.

Treatment

The treatment of post-transplantation bone loss should begin pre-transplantation[2]. All patients active on transplants waiting lists should be screened for bone disease, and biochemical abnormalities of CKD-MBD should be regularly monitored and treated. Patients should also be encouraged to take preventative measures against osteoporosis, such as cessation of smoking, reducing alcohol consumption and regular weight-bearing exercise.

Correction of biochemical abnormalities of CKD-MBD

Phosphate

Disordered mineral metabolism (hypophosphatemia, persistent hyperparathyroidism, low vitamin D levels and elevated FGF-23 levels) commonly occurs or persists post-transplantation[16]. Hypophosphatemia reflects elevated PTH and fibroblast growth factor 23 (FGF23) levels, as well as effects of calcineurin-inhibitor therapy. It may impair bone mineralization by impairing osteoblast proliferation and inducing apoptosis[17]. Conversely phosphate replacement has also been linked to a decrease in serum calcium, elevations in FGF23, and overall worsening of hyperparathyroidism[18]. Given that no studies demonstrate a clear benefit for phosphate replacement in this cohort, at present it seems justified to treat only severe hypophosphatemia.

Calcium and Vitamin D

Low serum 25(OH)D levels are common post-transplantation. Calcium levels are often decreased early, but commonly elevated at 3-6 months post-transplantation. Trials of vitamin D and calcium replacement post-transplantation have shown improvement in PTH levels, but conflicting effects on bone loss. Thus, calcium levels should be viewed in conjunction with other abnormalities of CKD-MBD, and calcium supplementation alone is seldom needed post-transplantation. Conversely vitamin D has beneficial effects on PTH, and may delay bone loss post-transplantation, and correction of low 25(OH)D levels is appropriate in most RTRs. However, in the face of severe ongoing hyperparathyroidism, this may predispose to hypercalcaemia.

Calcitriol and vitamin D receptor agonists (VDRAs)

Calcitriol and other VDRAs may prevent post-transplantation bone loss by increasing calcium absorption, promoting osteoblast differentiation and directly suppressing PTH, potentially counteracting some of the side-effects of steroids. Calcitriol use decreases PTH post-transplantation and increases BMD, but there is no clear benefit in reducing fractures[3]. However on the basis of this evidence, calcitriol has been used early post-transplantation to prevent bone loss, especially in those with concurrent hypocalcemia and reduced eGFR.

Cinacalcet and parathyroidectomy

Cinacalcet is currently not approved for use in RTRs, however it has been successfully used to treat persistent hypercalcemia and SHPT. In retrospective studies, cinacalcet use to treat SHPT post-transplantation was associated with improved BMD, and lower calcium and PTH levels[19,20]. However in a randomized-controlled trial of 114 RTRs, cinacaclet improved

hypophosphatemia and hypercalcemia, but did not improve BMD as compared to placebo[21]. Importantly there was no increase in adverse outcomes in the cinacalcet arm. Parathyroidectomy is performed in up to 5% of RTRs, largely for persistent SHPT or hypercalcemia. Parathyroidectomy does induce a marked fall in calcium and PTH and in retrospective studies in RTRs, parathyroidectomy has been associated with improved BMD at the hip and spine. A recent prospective trial comparing subtotal parathyroidectomy and cinacalcet in 30 RTRs, found that surgical intervention was associated with improved calcium control and BMD[22]. Given these findings, and the lack of a clear benefit of cinacalcet, it would seem difficult to recommend the use of cinacalcet in RTRs, other than as a bridging treatment before parathyroidectomy.

Immunosuppressive drug dosing

Glucocorticoids

Glucocorticoids increase post-transplantation bone loss by inhibiting bone formation and increasing bone resorption. Glucocorticoid reduction protocols are common however, these vary greatly between units. In general, glucocorticoid reduction or withdrawal has been associated with decreased bone loss, but fracture data are limited. In a large observational study of 77,430 RTRs who were followed for a median of 3.9 years, glucocorticoid withdrawal was associated with a 31% reduction in fracture risk, and the incidence of fractures was higher in those patients taking glucocorticoids when discharged [23]. In a smaller study of 175 solid organ transplants recipients, those with limited glucocorticoid exposure had similar fracture rates to those on conventional immunosuppressive protocols[24]. Glucocorticoid withdrawal in RTRs has also been associated with improved BMD parameters 1-year post-transplantation[25]. Of interest, a recent retrospective study comparing two patient cohorts transplanted 5-years apart, found a lower incidence of fractures in more recent RTR, despite there being less glucocorticoid withdrawal[26]. Steroid-sparing or withdrawal has the potential to improve bone loss post-transplantation, however this needs to be balanced against the potential risk of higher rates of rejection and warrants further investigation in prospective studies.

Anti-resorptive therapy

Bisphosphonates

Bisphosphonates are used in the treatment of osteoporosis, and cause an overall reduction in bone resorption by decreasing osteoclast activity. Their effects on BMD in RTRs have been the subject of numerous meta-analyses. The first, conducted in 2005, showed beneficial effects of bisphosphonates on BMD at the femoral neck and lumbar spine, but was inadequately powered to show a reduction in fracture risk[27]. The effect of bisphosphonates on bone loss and fractures during the first year after transplantation was examined in a meta-analysis of 11 studies and 780 RTRs[28]. There was an increase of around 3% in both femoral neck and lumbar spine BMD, and an overall reduction in fractures, but no significant reduction in vertebral fractures. Two recent meta-analyses re-examined this question in 2016 and both confirmed the results of earlier studies, showing improved BMD at the femoral neck and lumbar spine; however there no difference in fracture incidence[29,30].

Adynamic bone disease remains a concern with the use of bisphosphonates. Their use has been associated with an increase in biopsy-proven adynamic bone disease, although the effect of this finding on fracture incidence remains uncertain[31]. In the meta-analyses discussed above, bisphosphonate therapy was superior to VDRAs in preserving BMD, however the use of either therapy was beneficial when compared with no treatment. In summary, there are strong data that bisphosphonates prevent post-transplantation bone loss, however, this does not clearly extend to a reduction in fracture incidence. There are no comparative studies of different agents available for treatment of RTRs, who remain a heterogeneous population in terms of renal function. The efficacy and safety of these agents in patients with an eGFR <30 ml/min/1.73m^2 also remains unclear. Similarly, no consensus exists about duration of treatment. However, given that bone loss is greatest in the first 12 months, any benefit will be greatest in this period.

Denosumab

Denosumab is a fully human monoclonal antibody that inhibits receptor activator of nuclear factor kappa-B ligand (RANKL), and decreases the differentiation and activity of osteoclasts, reduces bone resorption and increases BMD. In a large study of osteoporotic women[15], denosumab improved BMD and decreased fracture risk, and was safe in those with reduced eGFR including CKD stages 3-4. However, its use in an end-stage kidney disease cohort was associated with severe hypocalcemia[32]. The safety of denosumab in RTRs was assessed in an open-label prospective study of 90 patients, in which denosumab was administered at baseline and 6-months[33]. There was an increase in BMD and a decrease in bone turnover markers, with no differences in serum calcium or eGFR between the two groups. While denosumab is a potential alternative to VDRAs and bisphosphonates in reducing post-transplantation bone loss, further studies are needed to demonstrate its safety in patients with reduced eGFR, as well as any beneficial effects on fracture risk in RTRs.

Conclusions

The post-transplantation period is associated with profound abnormalities of mineral metabolism, bone loss and fragility, which confer an increased fracture risk. Significant challenges remain in the screening and diagnosis of post-transplant bone loss and the largely opinion-based recommendations in the 2009 and current draft KDIGO CKD-MBD guidelines (http://www.kdigo.org/clinical_practice_guidelines/CKD-MBD%20Update/KDIGO%20CKD-MBD%20Update_Public%20Review_Final.pdf: last accessed 22 January 2017), accurately reflect the relative neglect of post-transplantation bone disease in clinical practice and the paucity of clinical evidence. It is widely acknowledged that the risk of post-transplantation fracture is higher; however we are poorly equipped to identify those who are at risk, and therefore those patients who may benefit from treatment. Furthermore there is little evidence to support the notion that treatment paradigms used in the general population can be simply and safely extrapolated to transplant recipients.

In clinical practice, use of DXA and biochemical markers such as ALP have some limited value and bone biopsy remains unavailable in most centres. Greater use of BSAP may aid clinical

practice, and newer BTMs and imaging techniques such as HRpQCT may one day offer the equivalent of a 'virtual bone biopsy'. However their use today remains largely experimental. Our inability to accurately diagnose and quantify post-transplantation bone disease (especially adynamic bone disease) poses challenges when considering treatment options. Initially these consist of the correction of common biochemical abnormalities of CKD-MBD. VDRAs, bisphosphonates and denosumab, which can improve BMD, but not necessarily fracture.

It seems prudent to include screening for bone disease in all transplant work-up algorithms, with a combination of BTMs, routine markers of CKD-MBD and DXA. Biochemical abnormalities should be treated and regularly reassessed, and any secondary causes addressed. RTRs with evidence of low bone mass should be considered for specific treatment with VDRAs or bisphosphonates. The duration of therapy is unknown, however, treatment for at least one year, with subsequent reassessment of BMD and BTMs seem reasonable. The role of glucocorticoid withdrawal remains unclear, and should only be considered in the context of other clinical and immunological parameters. Clinical judgement remains the cornerstone of what is becoming an increasingly challenging clinical problem. We believe that this provides a strong rationale for the formation of combined endocrinology and nephrology CKD-MBD clinics. These will not only facilitate patient care and clinical decision-making, but also the rapid translation of basic and clinical research into clinical practice.

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