Chapter 21: Transplant Bone Disease

(See KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder [CKD–MBD].)

21.1: In patients in the immediate post-kidney transplant period, we recommend measuring serum calcium and phosphorus at least weekly, until stable. *(1B)*

21.2: In patients after the immediate post-kidney transplant period, it is reasonable to base the frequency of monitoring serum calcium, phosphorus and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD. *(Not Graded)*

21.2.1: Reasonable monitoring intervals would be *(Not Graded)*:

- **In CKD stages 1–3T, for serum calcium and phosphorus, every 6–12 months; and for PTH, once, with subsequent intervals depending on baseline level and CKD progression.**
- **In CKD stage 4T, for serum calcium and phosphorus, every 3–6 months; and for PTH, every 6–12 months.**
- **In CKD stage 5T, for serum calcium and phosphorus, every 1–3 months; and for PTH, every 3–6 months.**
- **In CKD stages 3–5T, measurement of alkaline phosphatases annually, or more frequently in the presence of elevated PTH.**

21.2.2: In CKD patients receiving treatments for CKD–MBD, or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for efficacy and side effects. *(Not Graded)*

21.2.3: It is reasonable to manage these abnormalities as for patients with CKD stages 3–5. *(Not Graded)*

21.3: In patients with CKD stages 1–5T, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and interventions. *(2C)*

21.4: In patients with CKD stages 1–5T, we suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population. *(2C)*

21.5: In patients with an eGFR greater than approximately 30 mL/min/1.73 m^2, we suggest measuring BMD in the first 3 months after kidney transplant if they receive corticosteroids or have risk factors for osteoporosis as in the general population. *(2D)*

21.6: In patients in the first 12 months after kidney transplant with eGFR greater than approximately 30 mL/min/1.73 m^2 and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidiol, or bisphosphonates be considered. *(2D)*

21.6.1: We suggest that treatment choices be influenced by the presence of CKD–MBD, as indicated by abnormal levels of calcium, phosphorus, PTH, alkaline phosphatases, and 25(OH)D. *(2C)*

21.6.2: It is 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)*

21.6.3: There are insufficient data to guide treatment after the first 12 months. *(Not Graded)*

21.7: In patients with CKD stages 4–5T, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population and BMD does not predict the type of kidney transplant bone disease. *(2B)*

21.8: In patients with CKD stages 4–5T with a known low BMD, we suggest management as for patients with CKD stages 4–5 not on dialysis. *(2C)*

25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density; CKD, chronic kidney disease; CKD–MBD, chronic kidney disease–mineral and bone disorder; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; PTH, parathyroid hormone.

Background

We largely deferred to the KDIGO CKD–MBD Guideline that is pertinent to KTRs (684a). We reviewed these recommendations, but did not conduct independent evidence reviews.

Rationale

- The risk of fractures following kidney transplantation is high.
- It is not clear how to identify KTRs who might benefit from treatment.
- Bone disease is multifactorial, and most KTRs have preexisting CKD–MBD.
- In non-KTRs, low bone mineral density (BMD) or a loss of BMD predicts fractures, but data are scant for KTRs.
- No RCTs in KTRs have examined bone-specific therapies on patient-level outcomes, including mortality or fractures.
- Treatment with calcium, calcitriol or vitamin D analogs, and/or bisphosphonates has been suggested to improve BMD in KTRs.
- A small study of calcitriol demonstrated worsened bone turnover, but improved mineralization.
- A small study of treatment with bisphosphonates demonstrated worsening bone turnover and mineralization.
- There are insufficient data to suggest any bone-specific therapies after the first year of kidney transplantation.

CKD–MBD is common in KTRs. Most KTRs have some degree of CKD, and thus CKD–MBD may be present. Transplant-specific therapies, especially corticosteroids, may further affect CKD–MBD management. Biochemical abnormalities are common after transplantation. The scope and magnitude of the biochemical abnormalities of CKD–MBD fluctuate early, compared to late after transplantation. Posttransplant bone disease represents an important complication observed in a substantial proportion of patients, but the etiology and pathology vary. Early studies have demonstrated a rapid decrease in BMD in the first 6–12 months after successful kidney transplantation, and continued loss, albeit at a lower rate, for many years (685). Fractures are common and are associated with substantial morbidity.

The etiology of transplant bone disease is multifactorial. Patients come to transplantation with preexisting CKD–MBD. In addition, there are potentially deleterious effects of immunosuppressive agents (see Supporting Table 53 at http://www3.interscience.wiley.com/journal/118499698/toc), impaired kidney function, and other factors, such as postmenopausal status, presence of diabetes, smoking, physical inactivity and duration of CKD stage 5 (686). Previous studies in KTRs have shown a correlation between the cumulative dose of glucocorticoids and BMD. Based on a few bone biopsy studies in KTRs, glucocorticoids appear to be the primary determinant of subsequent bone volume and turnover. Thus, the cumulative and mean prednisone dose correlated negatively with bone turnover, whereas there was no correlation with CsA cumulative dose or serum parathroid hormone (PTH) (687). The possible role of CNIs remains incompletely studied, with contradictory reports on their effects on bone turnover (687).

Arterial calcification is also common after a kidney transplant, but it may be due to the effects of the uremic state and dialysis rather than the transplant itself. In KTRs (CKD stages 1–5T), only one prevalence study was identified, demonstrating a prevalence of calcification of 24.4% (444). Although this cross-sectional study was large (n = 1117), calcification was assessed by posterio-anterior plain abdominal X-ray examination of the aorto-iliac region, which is likely to be less sensitive than computerized tomography based imaging. In addition, one of the major difficulties in interpreting calcification in the transplant population is the carryover effect from CKD stage 5 or stage 5D. Currently, only one preliminary study is available suggesting that the progression of cardiovascular calcification may be halted after renal transplantation (688).

KTRs who develop persistently low levels of serum phosphorus (<1.0 mmol/L) should be considered for treatment with phosphate supplementation. However, phosphate administration is not without risk, and caution should be exerted, as it may exacerbate an already existing secondary hyperparathyroidism. Therefore, every attempt should be made in order to prescribe the strict minimum doses.

Although no clinical trials have specifically addressed the frequency of monitoring in KTRs, KTRs usually have CKD, and therefore are likely to have CKD–MBD. Thus, the management of the biochemical abnormalities of CKD–MBD after transplant should be similar to that proposed for non-transplant CKD and based on the prevalence of abnormalities, and the risks associated with those abnormalities.

A recent study of 303 KTRs in the United States found that 11–25% had abnormal calcium or calcium X phosphorus product in the first year following transplant, and 24% with eGFR 40–60 mL/min/1.73 m^2 had intact PTH levels >130 pg/mL (130 ng/L) at 1 year after kidney transplantation (689). Another series from the UK (690) evaluated 244 KTRs; 104 in the first year, and the remainder more than 1 year after transplant. Hypercalemia was present in 40% of recently transplanted recipients and 25% of long-term patients. Vitamin D insufficiency (40–75 nmol/L) was present in 29% and 43%, deficiency (12–39 nmol/L) in 56% and 46%, and severe deficiency (<12 nmol/L) in 12% and 5%, respectively. A larger cohort from Switzerland (691) evaluated 823 KTRs, on average 7 years after transplantation. They found only 27% had a PTH within normal range (i.e., 15–65 pg/mL [15–65 ng/L]), whereas 70% had hyperparathyroidism (PTH >65 pg/mL [65 ng/L]), and 2.8% were hypoparathyroid (PTH <15 pg/mL [15 ng/L]). Serum phosphorus was normal in 74% (0.85–1.45 mmol/L), and increased in only 3.6%. Finally, serum calcium was normal

in most patients (85.9%), with only 2.8% and 11.3% being hypo- and hypercalcemic, respectively. Thus, disorders of mineral metabolism may persist many years after transplantation.

There are few data describing the risk relationship of biochemical abnormalities of CKD–MBD and mortality in KTRs. A study of 773 KTRs found no relationship between serum calcium, phosphorus or PTH and mortality (692). However, patients with the highest quintile of phosphorus had increased risk of kidney allograft loss. Similarly, those with the highest quintile of calcium had an increased risk of kidney allograft loss.

Hypercalcemia following kidney transplantation is common and is usually due to hyperparathyroidism that persists from the preceding period of CKD. In 30–50% of KTRs, abnormal PTH secretion persists, causing hypercalcemia that may require parathyroidectomy (693–696). The same principles for managing patients with CKD stages 3–5 with CKD–MBD will apply for patients with CKD stages 3–5T.

Studies demonstrating that low BMD, or loss of BMD, predict fractures are lacking in KTRs. In one study (697), reductions in BMD have been associated with an increased fracture rate in studies of osteoporosis in postmenopausal women, in men, in patients treated with glucocorticoids, and in heart or liver transplant recipients. However, the etiology of posttransplant bone disease is likely influenced by pretransplant CKD–MBD, and ongoing CKD–MBD following transplantation, given that most patients have some impairment of CKD. Thus, studies in the general population and other solid-organ transplant recipients may not be applicable to KTRs.

Vitamin D

Trials evaluating vitamin D as preventive therapy assessed changes in BMD as the primary outcome. In two studies, an increase in BMD was observed with calcitriol and alfacalcidol, vs. 'no treatment' or placebo (698,699). Except for mild hypercalcemia in the study by Josephson et al. (700). there were few adverse effects. Unfortunately, there are no RCTs examining beneficial or harmful effects of bone-protective agents on patient-level outcomes, for example fractures, hospitalizations or mortality.

Bisphosphonates

Two studies have evaluated bisphosphonates in KTRs. Coco et al. (701) studied KTRs who received intravenous pamidronate at baseline, 1, 2, 3 and 6 months after transplantation. A rapid decrease of lumbar spine BMD was prevented in the pamidronate group. No changes in hip BMD were observed. There were no differences in the number of fractures between the groups after 1 year. Bone biopsies were done at the time of transplantation in 21 patients and in 14 patients after 6 months, six in the pamidronate group and eight in the control group (701). The mean activation frequency after 6 months was significantly lower in the pamidronate-treated patients than in the controls. All of the pamidronate-treated patients had adynamic bone disease on the 6-month biopsy; four patients with initial hyperparathyroidism and one with mixed uremic osteodystrophy developed adynamic disease. In the control group, three of eight had adynamic bone disease. Bone turnover improved in five of eight (62%) of controls and in none of the pamidronate biopsies. It worsened in one control biopsy (12%) and in five of six (83%) of pamidronate biopsies. Overall, the histology shows development of adynamic bone disease in the pamidronate-treated patients, but the results are limited by small numbers and short follow-up time. It is also not clear if the potential benefit from preserving bone volume outweighs the potential harm of decreased bone formation and/or prolonged mineralization.

Grotz et al. (702) evaluated intravenous ibandronate at baseline and 3, 6, and 9 months after transplantation. Loss of trabecular and cortical bone assessed by BMD was prevented by ibandronate. Fewer vertebral deformities by X-ray were observed in the ibandronate group compared to the controls. No significant side effects or decreased GFR were reported.

Overall, the quality of the preventive studies with bisphosphonates was ranked as moderate. Some of the studies showed limited fracture data and/or bone biopsy information. The observation in the study by Coco et al. that patients showed early evidence of and progression to adynamic bone disease should raise caution about the use of bisphosphonates in KTRs.

Only one RCT in KTRs late after transplantation evaluated the effect of calcitriol plus calcium carbonate vs. no treatment (703). This study enrolled 45 patients, with only 30 of them completing the trial. Bone biopsies were an evaluated end point. Although significant improvement in BMD was observed after 1 year in the treatment group, no differences were observed between the treatment and nontreatment groups. No fracture data were reported. Thus, the overall quality of the evidence is low. Bone biopsy results showed that bone turnover was better in 43% of the control biopsies and 12% of the calcitriol biopsies, but worse in 28% of the control biopsies and 50% of the calcitriol biopsies. No adverse effects were recorded.

Only one randomized comparison trial examined the effect of bisphosphonates in long-term KTRs with established osteopenia or osteoporosis. Jeffery et al. evaluated 117 patients with reduced BMD (T score ≤ -1). Patients were randomized to daily oral alendronate and calcium vs. calcitriol and calcium (704). One year of therapy was completed by 90 patients. Both treatments showed significant

increases in lumbar spine and femur BMD. No differences between groups were demonstrated.

Special considerations in children

In a four-arm study of 60 pediatric KTRs, alfacalcidol ± calcitonin was compared to alendronate with respect to BMD and selected biochemical markers (705). No differences were found. No fracture data were reported. Another 30 patients from the same investigators were given either alfacalcidol or placebo therapy, and BMD and selected biochemistries were assessed (706). There were no differences in outcomes. Given the paucity of data about CKD stages 1–5T, and the inherent inaccuracy in the use of dual energy X-ray absorptiometry to assess BMD in pediatric patients, there is currently insufficient evidence to recommend specific treatments for posttransplant renal bone disease in children.

Research Recommendations

- Observational studies are needed to determine the level of BMD that is predictive of fractures in KTRs.
- RCTs are needed in KTRs with low BMD at the time of transplantation to evaluate the effects of bisphosphonates or calcitriol and vitamin D analogs on patient-level outcomes, such as all-cause mortality, hospitalization, fracture, cardiovascular morbidity and mortality and quality of life.
- For KTRs with low serum calcidiol levels at the time of transplantation, RCTs are needed to determine the effect of vitamin D supplementation on change in BMD and patient-level outcomes, such as all-cause mortality, hospitalization, fracture, cardiovascular morbidity and mortality and quality of life.