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Management of Bone Disease in Kidney Transplant Recipients

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1. Introduction

There are several types of bone disease that are commonly seen in kidney transplant recipients. These include pre-existing uremic osteodystrophy, osteopenia, osteoporosis, bone fracture, osteonecrosis and bone pain syndrome (Brandenburg et al., 2004; Cohen et al., 2004; Julian et al., 1991; Zisman and Sprague, 2006). Kidney transplant recipients are now living longer than ever, and thus, proper prevention and management of bone disease has become an increasingly important part of their long-term care. Complications from post-transplant bone disease not only cause significant morbidity, but also increase the cost of care, hospitalization, and mortality (Abbott et al., 2001; Duriex et al., 2002; Jeffrey et al., 2003; Vatur et al., 2004; Zhang et al., 2008).

Bone disease after kidney transplant is a multifactorial process that includes continuing bone loss superimposed on pre-existing renal osteodystrophy (Brandenburg et al., 2004; Cohen et al., 2004; Zisman & Sprague, 2006; Zhang et al., 2008). There can be several different bone histologies and no single clinical biomarker can distinguish between the various bone disorders (Cruz et al., 2004; Cueto-Manzano et al., 2003; Monier-Faugere et al., 2000; Rolla et al., 2006). Bone biopsy, the gold standard for diagnosis and most accurate tool to guide clinical management is not commonly undertaken due to its invasive nature and difficulty with proper interpretation. The clinical disease spectrum includes four distinct phases: 1) pre-transplant osteodystrophy, 2) post-transplant bone loss exacerbated by a number of factors including immunosuppressive medications, 3) late stabilization with a functioning allograft, and 4) a return to uremic osteodystrophy when the renal allograft fails. This chapter will review the complex pathophysiology of the various types of bone diseases after kidney transplantation and explore the current evidence for their prevention and treatment.

2. Pre-existing uremic osteodystrophy

There are several different types of pre-existing renal osteodystrophy that may be encountered in kidney transplant patients including osteitis fibrosa cystica, adynamic bone disease, osteomalacia, osteopenia or osteoporosis.

2.1 Osteitis fibrosa cystica

Persistent secondary or tertiary hyperparathyroidism (HPT), reported in up to 30-50% of renal transplant patients, can lead to osteitis fibrosa cystica, a form of high turnover bone disease (Heaf et al., 2003). High bone turnover is usually associated with cortical bone loss and weakening its mechanical function (Malluche et al., 2010). Bone biopsy characteristically shows increased bone resorption, extensive osteoclastic activity and endosteal fibrosis (Malluche et al., 1994). High serum calcium (Ca), high phosphorus (Phos), low active vitamin D, high parathyroid hormone (PTH), and elevated alkaline phosphatase (AP) and osteocalcin are common. Alkaline phosphatase and osteocalcin are secreted by osteoblasts and can serve as useful clinical markers of high bone turnover. The cornerstone of treatment aims to suppress PTH secretion by a variety of methods including dietary phosphate restriction and use of phosphate binders, the use of the calcimimetic agent, cinacalcet, or surgical parathyroidectomy (Block et al., 2004; Chertow et al., 2002; Eknoyan et al., 2003; Teng et al., 2003).

2.2 Adynamic bone disease

This condition is usually caused by over-suppression of PTH and other growth factors, including gonadal hormones, growth hormone, and insulin-like growth hormone-1 (Brandenburg et al., 2004; Eknoyan et al., 2003; Zisman & Sprague, 2006). Bone biopsy findings include a low bone formation rate as assessed by tetracycline fluorescence-labeling, little or no evidence of cellular activity, a paucity of osteoblasts and osteoclasts, and thin osteoid seams (Malluche et al., 1994). Low bone turnover is frequently associated with loss of cancellous bone and abnormal mineral metabolic activity. Inability to maintain mineral homeostasis may contribute to cardiovascular and soft tissue calcifications, which may explain the high mortality rate in patients with low bone turnover (Malluche et al., 2010). Patients may have a high serum Ca, a relatively low PTH and low AP levels. Groups at highest risk include the elderly, diabetics, patients previously on peritoneal dialysis, those on calcium-containing phosphate binders, and those with over-suppressed PTH by vitamin D analogues. The prevention and treatment of adynamic bone disease is avoidance of over suppression of PTH secretion (Eknoyan et al., 2003). Historically, excessive aluminum accumulation was a major cause of adynamic bone disease in ESRD patients before the strict water purification and the avoidance of aluminum-containing phosphate binders were adopted (Zhang et al., 2008).

2.3 Osteomalacia

Osteomalacia in post-transplant patients has numerous causes including a deficit in bone mineralization due to hypophosphatemia, malnutrition, vitamin D deficiency, or aluminum toxicity (Brandenburg et al., 2004; Eknoyan et al., 2003; Zisman & Sprague, 2006). Characteristic findings on bone biopsy include wide unmineralized osteoid seams, low bone formation, absence of osteoblasts and osteoclasts and endosteal fibrosis (Malluche et al., 1994). Patients may have low serum Ca and Phos levels but PTH and AP levels are frequently within normal limits or slightly high. The gold standard for the diagnosis of osteomalacia from aluminum toxicity is aluminum staining of the bone biopsy (Eknoyan et al., 2003; Malluche et al., 1994). However, a useful, noninvasive clinical test in patients suspected to have chronic aluminum toxicity is desferoxamine stimulation of aluminum release. Treatments are targeted toward the underlying causes and include Ca and vitamin

D supplementations. The treatment of osteomalacia from aluminum toxicity is desferoxamine administration or kidney transplantation (Malluche et al., 1984; Zhang et al., 2008).

2.4 Osteopenia and osteoporosis

These conditions are usually diagnosed by bone mineral density (BMD) measurement with dual energy X-ray absorptiometry. Many patients undergoing transplant already have low bone mineral density. Thus, it is not surprising that low BMD (osteopenia and osteoporosis) is very common in kidney transplant recipients (Braun et al., 1999; Gallego et al., 2006). Common risk factors include older age, female gender, Caucasian race, chronic disease, immobility and malnutrition. In addition, hypogonadism is very common, but not routinely screened for or treated among the ESRD population. Chronic metabolic acidosis and uremic osteodystrophy can also contribute to bone loss (Brandenburg et al., 2004; Eknayan et al., 2003; Zisman & Sprague, 2006).

2.5 Other bone disease

Dialysis-related amyloidosis is caused by β_2 -microglobulin deposition as amyloid fibrils, leading to chronic inflammatory response, destructive arthropathy and lytic bone lesions. The articular symptoms associated with this disorder rapidly improve after renal transplantation. Although new cystic lesions are unusual, resolution of existing cysts is unusual (Zhang et al., 2008).

2.6 Clinical course

Patients often have a combination of the different type of bone diseases as described above, commonly termed mixed bone diseases. Due to the dynamic nature of renal osteodystrophy, it is not uncommon for one type of bone disease to evolve into another type of bone disease, depending on the clinical setting and management (Cohen et al., 2004; Eknayan et al., 2003; Zisman & Sprague, 2006).

The nature and evolution of pre-existing renal osteodystrophy after kidney transplant has yet to be fully established, largely due to a lack of serial histological studies by bone biopsy in this population. Several small studies do provide some insight into this issue. In a histological study of 20 patients who had bone biopsies before and 6 months after kidney transplant were compared (Cruz et al., 2004). Five of the 12 patients with adynamic bone disease recovered completely and the remaining cases had some improvement. Five of 8 patients with high-turnover bone disease developed low-turnover bone disease (4 with adynamic bone disease, 1 with osteomalacia). In a long-term study of 57 patients followed for a mean of 5.6 years after kidney transplant, 56% of patients were demonstrated to have decreased cancellous bone volume, 46% of patients had low bone turnover, and 59.7% of patients had reduced bone formation indices. High bone turnover was rarely seen, despite the fact that 63% of patients had elevated serum creatinine levels (monier-Faugere et al., 2000). In another report of 25 patients at least 5 years after transplant with good renal allograft function, bone biopsy revealed mixed bone disease in 10 patients, adynamic bone in 7 patients, high turnover bone in 4 patients, and normal bone in 3 patients (Cueto-Manzano et al., 2003). These studies suggest that pre-transplant renal osteodystrophy may not resolve completely, but often persists or evolves into a different disease process, depending on the allograft function, PTH level, immunosuppressive medications, and clinical management.

3. Post-transplant bone loss

During the first 6 to 12 months after kidney transplant, there is a rapid bone loss. After this time period, patients may either continue to lose bone at a slower rate, stabilize, or improve BMD depending on numerous factors including medication usage, overall health, and renal function (Brandenburg et al., 2004; Julian et al., 1991; Zisman & Sprague et al., 2006). A recent study reported 66% of patients with functioning renal allografts have osteopenia or osteoporosis (Gallego et al., 2006). Even after 20 years of kidney transplantation, 31% of patients had osteopenia and 41 % had osteoporosis (Braun et al., 1999). In another study of 63 kidney transplant recipients underwent yearly BMD measurements of the lumbar spine between 3 and 68 months posttransplant, BMD was significantly lower compared with healthy controls at all times. BMD measurements revealed a biphasic pattern. Between 3 and 10 months, a significant decrease in lumbar BMD occurred. However, no further significant bone loss was noted after the first year, and BMD remained relatively stable but at significantly lower levels compared with healthy controls (Brandenburg et al., 2004).

The possible causes of bone loss after kidney transplant are numerous and usually multiple factors are present in each patient. These factors include pre-existing continued uremic osteodystrophy as discussed above, immunosuppressive drugs, persistent HPT, hypophosphatemia, poor allograft function, loop diuretics, acidosis, smoking, alcohol abuse, hypogonadism, aging, chronic disease, physical inactivity/immobilization, and poor nutrition (Cohen et al., 2004; Cunningham, 2005; Gallego et al., 2006; Zisman & Sprague, 2006).

3.1 Immunosuppressive drugs

Rapid bone loss is very common in the first several months after kidney transplant, primarily caused by steroid usage, either as a large dose of steroids prescribed as a part of induction therapy or for the treatment of acute rejection episodes. The predominant effect of glucocorticoids on the skeleton is that of reduced bone formation. The decline in bone formation may be due to direct inhibition of osteoblast proliferation and increased apoptosis of osteoblasts and mature osteocytes. Glucocorticoids also increase bone resorption by increasing osteoclastogenesis. In addition, glucocorticoids decrease secretion of androgens and estrogens, primarily mediated by inhibition of gonadotropin secretion, and increase secretion of PTH (Brandenburg et al., 2004; Braun et al., 1999; Cunningham, 2005; Monier-Faugere et al., 2000; Van den Ham et al., 2003). There is some evidence that cyclosporine may increase bone turnover in animal study (Epstein, 1996). However, the effect of cyclosporine on bone metabolism in humans is less clear, being confounded by the presence of other illnesses or drugs that affect bone, particularly glucocorticoids. Tacrolimus appears to have less adverse effect on bone than cyclosporine (Marcen et al., 2006). The effects of other immunosuppressive medicines such as mycophenolate mofetil and sirolimus on bone remodeling remain unknown. The use of potent antibody induction therapy and modern maintenance agents can promote steroid-free or steroid-minimization protocol, which may exert protective effect on bone.

3.2 Hyperparathyroidism and hypercalcemia.

Elevated PTH levels usually decline, initially rapidly, then slowly after kidney transplant. About 30% of patients may still have elevated PTH levels beyond 1 year despite the presence

of normal renal function and vitamin D metabolism (Heaf et al., 2003). These patients likely have tertiary HPT due to the nodular transformation from a polyclonal hyperplasia into a monoclonal adenoma. The risk factors may include higher PTH level before transplant, longer time on dialysis and older age. Persistent HPT after transplant leads to continuing bone loss (Gallego et al., 2006; Heaf et al., 2003). A recent study of 201 transplant recipients reported a biphasic pattern of serum calcium levels with hypocalcemia immediately after kidney transplant and subsequent development of hypercalcemia (Evenepoel et al., 2009). It is well known that hypercalcemia can cause acute renal graft dysfunction from vascular constriction and volume depletion. Persistent hypercalcemia was shown to correlate with interstitial microcalcifications in renal graft and poor graft survival (Gwinner et al., 2005). Hypercalcemia can also cause calciphylaxis, neurological and other systemic symptoms. Persistent HPT, resorption of calcium deposits in soft tissues and normalization of active vitamin D metabolism likely contribute to the development of hypercalcemia after kidney transplant (Cunningham, 2005; Heaf et al., 2003; Kandil et al., 2010).

3.3 Hypophosphatemia

Renal phosphate wasting and hypophosphatemia are very common (up to 90%) in the early post transplant period, though they tend to resolve over time (Eknoyan et al., 2003; Levi, 2001). Persistent hyperparathyroidism and elevated phosphatonin fibroblast growth factor 23 (FGF23) are the main causes of hyperphosphaturia. Other possible causes include steroid therapy, reduced intestinal phosphorus absorption, reduced proximal tubular Na/Pi co-transporter expression or increased tubular sensitivity to PTH (Heaf et al., 2003; Levi, 2001; Zhang et al., 2008). Serum FGF23 level was found to be the best predictor of serum phosphate nadir after kidney transplant. The resolution of hyperphosphatoninism correlated with diminished renal phosphorus wasting 1 year after successful kidney transplant (Evenepoel et al., 2007, 2008). Phosphate supplements are usually given, but frequently are not effective in correcting severe hypophosphatemia. Administration of calcimimetic agent cinacalcet was reported to significantly decrease renal phosphate wasting, which was associated with suppressed serum PTH level, but not FGF23 level (Serra et al., 2008). Interestingly, dipyridamole can improve renal tubular phosphate reabsorption and increase serum phosphate levels in these patients (Balal et al., 2005).

3.4 Vitamin D receptor (VDR) genotype.

There are several variants and genotypes of the VDR reported. Compared with Bb and BB alleles, the bb allele was associated with a significantly increased recovery of BMD from 3 to 12 months after kidney transplant with a 7% of BMD increase in lumbar spine. More rapid resolution of both HPT and histological osteitis fibrosa after kidney transplant was also documented in patients with the “favorable” VDR bb allele (Torres et al., 1996).

3.5 Hypogonadism

The majority of ESRD patients are hypogonadal and gonadal hormones remain low in both female and male patients after kidney transplant. Steroids have been suggested to play a role. Reports show that about 50 % of male patients have low testosterone levels after kidney transplant. Aging and postmenopausal status worsen bone loss and increase the risk of bone fracture after kidney transplant (Cunningham, 2005; Cohen et al., 2004; Eknoyan et al., 2003; Epstein, 1996; Zisman & Sprague, 2006).

4. Prevention and treatment of bone loss

The 2009 Kidney Disease: Improving Global Outcome (KDIGO) clinical practice guideline provides recommendations for the evaluation, prevention, and treatment of bone disorder in renal transplant patients (KDOQI, 2009). The same measures that are used to prevent osteoporosis in the general population also apply to transplant recipients. General recommendations should include the following: all patients should receive counseling regarding smoking cessation, early mobilization after transplantation and fall prevention.

4.1 Vitamin D

Vitamin D deficiency (e.g., 25-hydroxyvitamin D level less than 20 ng/ml) is very common in kidney patients, including CKD, ESRD and kidney transplant recipients. Large dose vitamin D (50,000 units of vitamin D2 or D3) given weekly is more effective than the over-the-counter low dose vitamin D in correcting deficiency. Despite of the successful kidney transplant, the active 1, 25 hydroxyvitamin D levels are lower than the expected (Fleseriu & Licata, 2007). Correcting vitamin D deficiency by supplement can increase the serum level of active 1, 25 hydroxyvitamin D (Amin et al., 2007). After kidney transplantation, all patients should receive 1000 mg/day of calcium and 800 IU/day of vitamin D in absence of hypercalcemia (Cunningham, 2005; Cohen et al., 2004; 2003; Epstein, 1996; Torres et al., 2004; Zisman & Sprague, 2006). Studies have found that BMD increases in treated patients and decreases in untreated patients, with a difference of 6-7% being seen 1 year after kidney transplant. Active vitamin D calcitriol or its analogues should be considered when a patient has a GFR of < 30 ml/min, secondary HPT or malabsorption. Serum Ca, Phos and PTH levels need to be monitored periodically and the dose of vitamin D adjusted accordingly (Jeffery et al., 2003; Torres et al. 2004). The other benefic effects of vitamin D on immune system and cardiovascular health are being elucidated. It is with the hope that vitamin D may have the potential for reducing infectious complications while decreasing the risk of rejection after kidney transplant.

4.2 Gonadal hormones

Many premenopausal women and men undergoing solid organ transplantation have hypogonadism, most often related to the effects of glucocorticoids and chronic illness. In men and women undergoing transplantation, testosterone and estrogen-progestin replacement, respectively, have been shown to slow bone loss (Eknoyan et al. 2003; Cunningham, 2005). Hormonal replacement therapy (HRT) or selective estrogen-receptor modulators should be used for postmenopausal recipients after kidney transplant if there is no contraindication. Testosterone may also be considered for men with documented hypogonadism and osteoporosis (Eknoyan et al. 2003; Cunningham, 2005; Zhang et al., 2008).

4.3 Parathyroidectomy

After kidney transplant, HPT frequently undergoes spontaneous regression as both renal function and vitamin D metabolism return to normal. However, as many as 30% of patients may have persistently high PTH levels, often due to the development of a nodular monoclonal adenoma (Heaf et al., 2003). About 5% of kidney transplant recipients, with a reported range of 1 to 20%, undergo a surgical parathyroidectomy. The indications for surgery vary among the transplant centers, but the two major indications for

parathyroidectomy in renal transplant patients are severe symptomatic hypercalcemia (> 11.5 mg/dl), usually occurring in the early post transplant period, and persistent hypercalcemia more than 1 year after transplant (Kandil et al., 2010; Zhang et al., 2008). BMD usually increases after surgical correction of HPT (Eknoyan 2003; Heaf et al., 2003; Jeffery et al., 2003; Levi, 2001). Parathyroidectomy was reported to be associated with an inferior graft function and worsening graft survival (Schwarz et al., 2007; Schmid et al., 1997). We retrospectively analyzed 794 kidney transplants performed at our center with at least 3 years of follow-up, 49 of them had persistent HPT after kidney transplant. Patients with HPT and non- HPT had similar 3-year graft survival. Parathyroidectomy was associated with a decreased estimated glomerular filtration rate at 3 years. However, there was no statistical difference in 3-year graft survival. Our experience suggests that parathyroidectomy is a safe and effective therapy for persistent HPT in renal transplant recipients (Kandil et al., 2010).

4.4 Calcimimetics

Cinacalcet, a calcimimetic compound, has been increasingly studied and used to treat persistent HPT and its associated hypercalcemia after kidney transplant. All studies in transplant patients have found that serum calcium concentration decreases with cinacalcet therapy (Black et al., 2003; El-Amm et al., 2007; Kamar et al., 2008; Kruse et al., 2005; Leca et al., 2006; Serra et al., 2005; Srinivas et al., 2006; Szwarc et al., 2006). However, the effect of cinacalcet on PTH and serum phosphorus levels varies across studies with no decrease in PTH level reported in two studies, while PTH decreased in the rest. Serum phosphorus level increased in most and did not change in three studies (Kruse et al., 2005; Srinivas et al., 2006). A recent study of 9 patients reported a favorable effect of cinacalcet on BMD (Bergua et al., 2008). Although large studies from dialysis patients demonstrate its safety, there is limited data in transplant patients. Cinacalcet was found to have moderate effect on tacrolimus pharmacokinetics, but not on cyclosporine or mycophenolate in renal transplant recipients (Falck et al., 2008). Thus, cinacalcet is not officially approved for usage in transplant patients yet.

4.5 Minimizing steroids

It is recommended to rapidly taper to a maintenance dose of 5 -7.5mg of prednisone daily, if possible, to minimize the bone loss and osteotoxic effects. Further, steroid-free protocols should be considered for patients with pre-transplant osteopenia or osteoporosis (Braun et al., 1999; Cunningham, 2005; Gallego et al., 2006; Van de Ham et al., 2003). Steroid withdrawal at 6 months has been reported to improve BMD at 1 year after kidney transplant. However, this was done in highly selected adult patients. There is no good data that later steroid withdrawal (after 1 year) is beneficial for the purpose of bone building (Eknoyan et al., 2003; Epstein, 1996). Recently, a prospective study comparing steroid -free and steroid-treated children found that the BMD Z-scores significantly decreased in steroid-free groups with or without prophylaxis with vitamin D analogue alphacalcidol. However, steroid-treated group, who also received ibandronate prophylaxis, maintained BMD Z-scores over 2 year of follow-up (Grenda et al., 2011).

4.6 Bisphosphonates

Bisphosphonate therapy, that increases osteoclast apoptosis and reduces active osteoclasts and bone resorption, has been widely used to treat postmenopausal and steroid-induced

osteoporosis. There are consistent studies reporting that it can also effectively prevent and treat bone loss in kidney transplant recipients. A BMD difference of up to 9% has been reported after 1 year's treatment compared with control group without bisphosphonate treatment (Coco et al., 2003; Fan et al., 2003; Hass et al., 2003). In addition, in a follow-up study of 4 years, intravenous pamidronate (0.5mg/kg) given at the time of transplant and at 1 month later could provide long-term protection of BMD (Fan et al., 2003). However, adynamic bone disease was commonly observed after bisphosphonate treatment (Coco et al., 2003). Low turnover bone diseases are common in dialysis patients and additional suppression of bone remodeling without stimulation of new bone formation may not improve the mechanical strength and quality of bone (Coco et al., 2003; Cruz et al., 2004; Zhang et al., 2008). This may explain why the prevention of bone loss with bisphosphonates has not been shown to effectively decrease bone fracture rate in kidney transplant recipients yet.

4.7 Calcitonin

Although calcitonin is effective in preventing bone loss in postmenopausal women, its effectiveness in post-transplant bone loss is uncertain. One report noted that intranasal salmon calcitonin 200 IU every other day can prevent early bone loss as effectively as alendronate and alfacalcidol in renal transplant recipients (El-Agroudy et al., 2005). But other studies have failed to demonstrate superiority to calcium supplementation in transplant recipients (Bone et al., 2004; Palmer et al., 2005; Valimaki et al., 1999).

4.8 Teriparatide

Recombinant human parathyroid hormone (PTH, teriparatide) has been shown to improve BMD in patients with glucocorticoid-induced and postmenopausal osteoporosis (Black et al., 2003; Neer et al., 2001). It has been approved by the FDA for treating osteoporosis in general population, but not in organ transplant patients. A recent study of 26 kidney transplant recipients with daily teriparatide injections demonstrated a stabilization of BMD in the femoral neck and increased cortical width. But there was no improvement in bone turnover or bone mineralization as measured by histology (Cejka et al., 2008). Thus, its use in this setting remains experimental.

5. Post-transplant bone fracture

Bone fracture is a devastating complication for transplant patients. It impairs their quality of life, increases the cost of care and hospital stay, and may even cause death. Common fracture sites are the legs, vertebral bodies, hips and ribs (Abbott et al., 2001; Nisbeth et al., 1999; Vautour et al., 2004). The risk of fracture is greatest in the first 6 months after kidney transplant, but continues over the long term, as bone loss slows 6-24 months after transplantation (Vautour et al., 2004). The cumulative bone fracture rate has been reported as high as 17 to 20% (Abbott et al., 2001; Nisbeth et al., 1999; Vautour et al., 2004). Higher fracture rates are seen in the elderly, females, diabetics, and simultaneous kidney pancreas transplant recipients (Abbott et al., 2001; Nisbeth et al., 1999; Vautour et al., 2004). The high bone fracture rate is thought to be the consequence of continuing bone loss that is superimposed on preexisting uremia osteodystrophy. Development of osteoporosis places kidney transplant recipients at increased risk for bone fractures (Brandenburg et al., 2004; Cohen et al., 2004; Cunningham, 2005). It is important to note that no medicine has been proven to decrease fracture risk in the kidney transplant patients yet.

6. Osteonecrosis

Osteonecrosis or avascular necrosis commonly affects the femoral head, knee, shoulder or elbow, and usually appears 6 to 24 months after kidney transplant. It is characterized by the ischemic death of bone marrow cells and osteocytes and loss of trabeculae. Clinical presentation is mainly joint pain that worsens with weight bearing. It may affect up to 15% of kidney transplant recipients (Lausten et al., 1998). In a cohort study of over 42,000 kidney recipients, the cumulative incidence of hospitalization for osteonecrosis was 7.1 episodes per 1,000 patient-years (Abbott et al., 2002). Steroid usage, especially a high cumulative dose of steroid or pulse steroid therapy is implicated as the main etiology. Other risk factors are pre-existing bone disease, diabetes and lupus nephritis (Abbott et al., 2005; Teng et al., 2000). The best diagnostic test for avascular necrosis is MRI, as plain film X-rays and bone scanning are less sensitive. Treatment includes resting, core decompression, vascularized bone grafts, or joint replacement, depending on the clinical severity.

7. Post-transplant bone pain syndrome

About 10 to 20% of transplant recipients experience bone pain, usually diffuse, particularly in the lower extremities. Both of the calcineurin inhibitors, cyclosporine and tacrolimus, have been implicated as the possible cause (Goffin et al., 2003; Grotz et al., 2001). Calcium channel blockers have been demonstrated to reduce bone pain (Barbarosa et al., 1995; Goffin et al., 2003). This suggests that calcineurin inhibitor-associated intraosseous vasoconstriction and ischemia may underlie the pathophysiology of this syndrome.

8. Clinical approach

Therapy for post-transplant bone disease needs to be individualized with physicians assessing the risk factors of bone loss in each patient and creating a plan for long-term bone care. It is recommended that a baseline BMD should be documented before or at the time of kidney transplant, with the BMD being repeated at 3 to 6 months after transplantation and then every 12 months for those with an abnormal BMD (Brandenburg et al., 2004; Cohen et al., 2004; Cunningham, 2005; Eknayan et al., 2003).

All patients should be screened for vitamin D deficiency. Vitamin D deficiency or insufficiency should be treated with large dose of regular vitamin D, which follows with a maintenance dose of vitamin D supplement. All patients should receive counseling regarding smoking cessation, early mobilization after transplantation, and fall prevention. For patients with baseline BMD consistent with osteopenia or osteoporosis, calcium and vitamin D supplements should be started after kidney transplant. Further, all patients with evidence of hypogonadism should receive HRT if it is not contraindicated. Bisphosphonate should be considered and used with caution for patients with baseline osteoporosis, a history of fracture with minimal trauma, or at high risk for fracture. If baseline BMD is normal, then calcium, vitamin D and HRT should be considered as prophylaxis of bone loss in high-risk patient groups such as the elderly, diabetics, or combined kidney and pancreas transplant recipients.

If BMD is declining after transplant from baseline despite calcium, vitamin D and HRT, then bisphosphonates or calcitonin may be considered. We suggest bisphosphonates, rather than calcitonin, as there is more efficacy data with bisphosphonates. Both oral and intravenous

bisphosphonates have been shown to be effective in this setting. The decision should be based upon individual patient preferences and ability to take oral medications. Calcitonin can replace bisphosphonates if patients can't tolerate bisphosphonates or if they are contraindicated clinically. Persistent HPT should be treated with cinacalcet or parathyroidectomy surgery. Other measures include: lowering the dosages of, or discontinuing steroid if possible; treating metabolic acidosis; treating hypophosphatemia and hypocalcaemia; and limiting alcohol intake. With a failing renal allograft, patients should be managed in the same manner as any other CKD patient for recurring mineral and bone disorders, including uremic osteodystrophy.

9. Conclusion

Despite successful prevention of bone loss after transplant with several different types of medications, this effect has not resulted in the reduction of bone fracture as of yet. The bone diseases after kidney transplant have a complicated pathophysiology and various types of histology. Their clinical management is challenging and requires a comprehensive approach to address the underlying and ongoing disease processes. Bone biopsy with histomorphometric analysis is the best way to define the type of disease process and to guide our clinical management. More studies with the goal of restoring the normal bone remodeling and improving bone quality and strength are needed, so that the high incidence of fracture can be successfully decreased in kidney transplant recipients.

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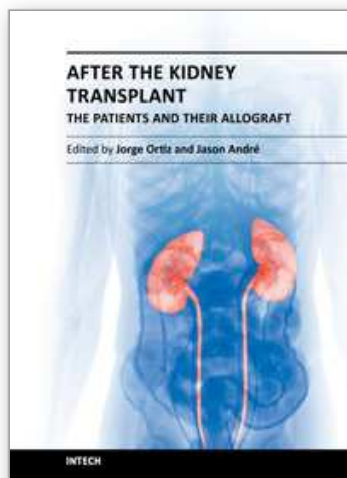
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There are many obstacles in kidney transplantation. For the transplant team, there is the balance between immunosuppression to aid in the recipient's tolerance of the allograft and the infection risk of a suppressed immune system. These potential long term complications of kidney transplantation are relatively well known, but there are many other complications that patients and families do not consider when preparing themselves for a kidney transplant. Although the benefits of attempting a kidney transplant far outweigh downfalls of the long term sequelae, kidney transplantation is by no means a benign procedure. It is the hope of these authors that the reader will leave with a sense of understanding towards the kidney recipients.

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