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REVIEW

Metabolic bone diseases in kidney transplant recipients

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Abstract

Metabolic bone disease after kidney transplantation has a complex pathophysiology and heterogeneous histology. Pre-existing renal osteodystrophy may not resolve completely, but continue or evolve into a different osteodystrophy. Rapid bone loss immediately after transplant can persist, at a lower rate, for years to come. These greatly increase the risk of bone fracture and vertebral collapse. Each patient may have multiple risk factors of bone loss, such as steroids usage, hypogonadism, persistent hyperparathyroidism (HPT), poor allograft function, metabolic acidosis, hypophosphatemia, vitamin D deficiency, aging, immobility and chronic disease. Clinical management requires a comprehensive approach to address the underlying and ongoing disease processes. Successful prevention of bone loss has been shown with vitamin D, bisphosphonates, calcitonin as well as treatment of hypogonadism and HPT. Novel approach to restore the normal bone remodeling and improve the bone quality may be needed in order to effectively decrease bone fracture rate in kidney transplant recipients.

Key words: Uremic osteodystrophy; Bone loss; Fracture; Kidney transplantation

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INTRODUCTION

Metabolic bone diseases in kidney transplant recipients may include pre-existing uremic osteodystrophy, osteoporosis, bone fracture, osteonecrosis and bone pain syndrome. Complications from bone disease not only cause significant morbidity, but also increase the cost of care, hospitalization, and mortality[1-3]. Kidney transplant recipients are now living longer than ever, and thus, proper management of bone disease has become an increasingly important part of their care. The pathophysiologic process of bone disease may be divided into four phases: (1) pre-transplant osteodystrophy; (2) post-transplant bone loss exacerbated by immunosuppressive medication; (3) late stabilization with a functioning allograft; and (4) a return to uremic osteodystrophy when the renal allograft fails.

PRE-EXISTING UREMIC OSTEODYSTROPHY

Several different types of renal osteodystrophy can be encountered in kidney transplant patients. They are osteitis fibrosa cystica, adynamic bone disease, osteomalacia, osteoporosis and dialysis related amyloidosis.

Osteitis fibrosa cystica

Persistent secondary or tertiary hyperparathyroidism (HPT), reported in up to 30%-50% of renal transplant patients, can cause osteitis fibrosa cystica, a form of high turnover bone disease[4]. It is associated with cortical bone loss and weakening its mechanical function[5]. Bone biopsy characteristically shows increased bone resorption, extensive osteoclastic activity and endosteal fibrosis[6]. High levels of serum parathyroid hormone (PTH), calcium (Ca), phosphorus (Phos), alkaline phosphatase (AP) and osteocalcin are common. AP and osteocalcin are secreted by osteoblasts and can serve as useful marker of high bone turnover[7-9]. The cornerstone of treatment aims to suppress PTH secretion by dietary phosphate restriction, use of phosphate binders and calcimimetic agent (cinacalcet), or surgical parathyroidectomy.

Adynamic bone disease

Historically, excessive aluminum accumulation was a major cause of adynamic bone disease in dialysis patients before the strict water purification and the avoidance of aluminum-containing phosphate binders were adopted[3]. Now, it is usually caused by over-suppression of PTH and other growth factors[8,10,11]. Bone biopsy findings include a low bone formation rate as assessed by tetracycline fluorescence-labeling, little or no cellular activity (paucity of osteoblasts and osteoclasts) and thin osteoid seams[6]. It is associated with loss of cancellous bone and abnormal mineral metabolic activity. Inability to maintain mineral homeostasis contributes to cardiovascular and soft tissue calcifications, which may explain the high mortality rate in patients with adynamic bone disease[5]. Patients may have a high serum Ca, a relatively low PTH and AP levels. Groups at highest risk include the elderly, diabetics, peritoneal dialysis patients, those on calcium-containing phosphate binders and with over-suppressed PTH by vitamin D analogues[8]. The prevention and treatment of adynamic bone disease is avoidance of over suppression of PTH secretion.

Osteomalacia

Osteomalacia is characterized by a deficit in bone mineralization due to hypophosphatemia, malnutrition, vitamin D deficiency or aluminum toxicity[11,12]. Characteristic findings on bone biopsy include wide unmineralized osteoid seams, low bone formation, absence of osteoblasts and osteoclasts[6]. 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. However, desferoxamine stimulation of aluminum release is frequently used as it is noninvasive[6,8]. Treatments are targeted towards the underlying causes and include the supplementation of Ca, Phos and vitamin D. The treatment of osteomalacia from aluminum toxicity is desferoxamine administration or kidney transplantation[3,13].

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 BMD. 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 also contribute to bone loss[8,10,11].

Dialysis-related amyloidosis

It is caused by β_2-microglobulin deposition as amyloid fibrils, leading to chronic inflammatory response, destructive arthropathy and lytic bone lesions. The articular symptoms can rapidly improve after renal transplantation. Although developing new cystic lesion is rare, resolution of existing cysts is unusual[3].

CLINICAL EVOLUTION OF UREMIC OSTEODYSTROPHY

Patient may have a combination of different type of bone diseases, commonly termed mixed bone diseases. Due to the dynamic nature, it is not uncommon for one type of bone disease to evolve into another type, depending on the clinical setting and management[8,11,14]. The nature and evolution of pre-existing renal osteodystrophy after kidney transplant has yet to be fully established, largely due to lack of serial histological studies by bone biopsy in this population. In a histological study of 20 patients who had bone biopsies before and 6 mo after kidney transplant, 5 of the 12 patients with adynamic bone disease recovered completely and the remaining 7 cases had some improvement, 5 of 8 patients with high-turnover bone disease developed low-turnover bone disease including 4 with adynamic bone disease and 1 with osteomalacia[15]. In a long-term study of 57 patients followed for a mean of 5.6 years after kidney transplant, 56% of patients had 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 graft dysfunction[16]. In another report of 25 patients with good graft function, bone biopsy at least 5 years after transplant revealed mixed bone disease in 10 patients, adynamic bone in 7 patients, high turnover bone in 4 patients, and normal bone in only 3 patients[17]. These studies suggest that pre-transplant renal osteodystrophy may not resolve completely, but often persists or evolves into a different type of disease, depending on the patient medical condition, graft function and treatment.

POST-TRANSPLANT BONE PAIN SYNDROME

About 10% to 20% of transplant recipients experience

bone pain, usually deep and diffuse, particularly in the lower extremities. Both of the calcineurin inhibitors, cyclosporine and tacrolimus, have been implicated as the cause[18,19]. Calcium channel blockers have been demonstrated to reduce bone pain[18,20]. This suggests that calcineurin inhibitor-associated intraosseous vasoconstriction and ischemia may underlie the pathophysiology of this syndrome.

POST-TRANSPLANT OSTEONECROSIS

Osteonecrosis or avascular necrosis commonly affects the femoral head, knee, shoulder or elbow, and usually appears 6 to 24 mo 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[21]. In a cohort study of over 42 000 kidney recipients, the cumulative incidence of hospitalization for osteonecrosis was 7.1 episodes per 1000 patient-years[22]. Steroids usage, especially a high cumulative dose of steroids or pulse steroids therapy is implicated as the main etiology. Other risk factors include pre-existing bone disease, diabetes and lupus nephritis[23,24]. The best diagnostic test for avascular necrosis is magnetic resonance imaging, 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.

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. The risk of fracture is greatest in the first 6 mo after kidney transplant, but continues over the long term[2]. The cumulative bone fracture rate has been reported as high as 17% to 20%, and higher fracture rates are seen in the elderly, females, diabetics, and simultaneous kidney pancreas transplant recipients[2,25,26]. Post-transplant bone fracture is thought to be the consequence of continuing bone loss that is superimposed on preexisting uremic osteodystrophy[10,14,27].

POST-TRANSPLANT BONE LOSS

During the first 6 to 12 mo after kidney transplant, there is a rapid bone loss. After that, patient may either continue to lose bone at a slower rate, stabilize, or improve BMD depending on numerous factors including medication usage and renal function[10,11]. A study reported 66% of patients with functioning grafts have osteopenia or osteoporosis[28]. In another study, 63 patients underwent yearly BMD of the lumbar spine between 3 and 68 mo post transplant, it revealed a biphasic pattern. Between 3 and 10 mo, a significant decrease in lumbar BMD occurred. However, no further bone loss was noted after the first year, and BMD remained relatively stable but at significantly lower level compared with healthy controls[10].

The causes of bone loss after kidney transplant are numerous and usually multiple factors are present in each patient. These factors include continued pre-existing uremic osteodystrophy, immunosuppressive drugs, persistent HPT, hypophosphatemia, loop diuretics, graft dysfunction, metabolic acidosis, smoking, alcohol abuse, hypogonadism, aging, physical inactivity/immobilization and poor nutrition[11,14,27,28].

Immunosuppressive drugs

Rapid bone loss in the first several months after kidney transplant is primarily caused by steroids usage. The predominant effect of glucocorticoids on the skeleton is that of reduced bone formation by inhibiting osteoblast proliferation and increasing apoptosis of osteoblasts. Glucocorticoids also increase bone resorption by increasing osteoclastogenesis. In addition, they decrease secretion of androgens and estrogen[10,16,27]. Cyclosporine increase bone turnover in animal study[29]. However, its effect on bone metabolism in humans is less clear. Tacrolimus appears to have less adverse effect on bone than cyclosporine[30]. The effects of mycophenolic acid, sirolimus, everolimus and belatacept on bone remodeling remain unknown. The use of potent antibody induction and modern maintenance agents can promote steroid-free or steroid-minimization protocol, which may exert protective effect on bone.

HPT and hypercalcemia

Elevated PTH level usually declines, initially rapidly, then slowly after kidney transplant. About 30% of patients may still have elevated PTH levels beyond 1 year, despite the normal renal function and vitamin D metabolism[4]. These patients likely have tertiary HPT due to nodular transformation from polyclonal hyperplasia into monoclonal adenoma. Persistent HPT leads to continuing bone loss[4,28]. A study of 201 transplant recipients reported a biphasic pattern of serum calcium levels with hypocalcemia immediately after kidney transplant and subsequent development of hypercalcemia[31]. It is well known that hypercalcemia can cause acute graft dysfunction from vascular constriction. Persistent hypercalcemia was shown to correlate with interstitial microcalcifications in renal graft and poor graft survival[32]. Hypercalcemia can also cause calciphylaxis, neurological and other 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[4,27,33].

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[8,34]. Persistent HPT and elevated phosphotonin and fibroblast growth factor 23 (FGF23) are the main causes of hyperphosphaturia. Other causes include steroids therapy, reduced intestinal absorption, reduced proximal tubular Na/Pi co-transporter expression or increased tubular sensitivity to PTH[4,34]. 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 kidney transplant[35,36]. Phosphate supplements are usually given, but frequently are not effective in correcting severe hypophosphatemia. Cinacalcet was reported to significantly decrease renal phosphate wasting, which was associated with suppressed serum PTH level, but not FGF23 level[37]. Interestingly, dipyridamole was reported to improve renal tubular reabsorption of phosphate and increase serum phosphate level[38].

Vitamin D receptor genotype

There are several genotypes of the Vitamin D receptor (VDR) reported. Compared with Bb and BB alleles, the bb allele was associated with a better recovery of BMD from 3 to 12 mo 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[39].

Hypogonadism

The majority of ESRD patients are hypogonadal and gonadal hormones remain low after kidney transplant. Steroids have been suggested to play a role. 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[8,11,14,27].

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[40]. All patients should be evaluated for the pre-existing bone disease as well as the ongoing risk factors of bone loss. A comprehensive approach is needed to target on the underlying and ongoing pathological processes.

Minimizing steroids

It is recommended to rapidly taper to a maintenance dose of 5 mg of prednisone daily, if possible, to minimize the bone loss. Further, steroid-free protocol should be considered for patients with pre-transplant osteopenia or osteoporosis[27,28,41]. Recent analysis based on the United States Renal Data System found that early steroid withdrawal at hospital discharge was associated with a 31% fracture risk reduction and lower fracture related hospitalization[41]. Steroid withdrawal at 6 mo was also reported to improve BMD at 1 year after kidney transplant. However, this was done in highly selected patients. There is no data supporting that later steroid withdrawal (after 1 year) is beneficial for the purpose of bone building[8,29]. Recently, a prospective study comparing steroid-free and steroid-treated children found that the BMD significantly decreased in steroid-free groups with or without prophylaxis with alphacalcidiol. However, steroid-treated group, who also received ibandronate prophylaxis, maintained BMD over 2 years of follow-up[42].

Vitamin D

Vitamin D deficiency (25-hydroxyvitamin D level less than 20 ng/mL) is very common in kidney patients. Large dose vitamin D (50 000 units of vitamin D2 or D3) given weekly is more effective than the maintenance dose vitamin D in correcting deficiency. Despite successful kidney transplant, the active 1, 25 dihydroxyvitamin D level is lower than the expected[43]. Vitamin D supplement can increase the serum active 1, 25 dihydroxyvitamin D level[44]. All patients at risk should receive 1000 mg/d of calcium and 800 IU/d of vitamin D in absence of hypercalcemia[11,14,27,45]. 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[1,45]. The other benefic effects of vitamin D on immune system and cardiovascular health are being elucidated.

Gonadal hormones

Hormonal replacement therapy (HRT) or selective estrogen-receptor modulators should be used for postmenopausal women after kidney transplant if there is no contraindication. Testosterone should be considered for men with documented hypogonadism and osteoporosis[3,8,27]. Testosterone and estrogen replacement, respectively, have been shown to slow bone loss in kidney transplant recipients[8,27].

Calcimimetics

Cinacalcet has been studied to treat persistent HPT and hypercalcemia after kidney transplant. All studies have found that serum calcium concentration decreases with cinacalcet therapy. However, the effect of cinacalcet on PTH and serum phosphorus levels varies across studies[46-49]. A recent study of 9 patients reported a favorable effect of cinacalcet on BMD[50]. Cinacalcet was shown to have moderate effect on tacrolimus pharmacokinetics, but not on cyclosporine or mycophenolic acid[51].

Parathyroidectomy

About 5% of kidney transplant recipients, with a reported range of 1% to 20%, undergo a surgical parathy-

roidectomy[3,33]. The indications for surgery vary, the two major ones 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. BMD usually increases after surgical correction of HPT[1,4,8,34]. Parathyroidectomy was reported to be associated with an inferior graft function and poor graft survival[52,53]. 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 transplant. Patients with HPT and non-HPT had similar 3-year graft survival. Parathyroidectomy was associated with a decreased GFR 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[33].

Bisphosphonates

Bisphosphonates increase osteoclast apoptosis and reduce bone resorption. Bisphosphonates have been widely used to treat postmenopausal and steroid-induced osteoporosis. There are consistent data showing bisphosphonate therapy 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[54-56]. In addition, intravenous pamidronate (0.5 mg/kg) given at the time of transplant and at 1 mo could provide long-term protection of BMD in a follow-up study of 4 years[55]. However, adynamic bone disease was commonly observed after bisphosphonate treatment[54]. Low turnover diseases are common in dialysis patients and additional suppression of bone remodeling without stimulation of new bone formation will not improve the mechanical strength and quality of bone[3,15,54]. 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.

Calcitonin

Although calcitonin is effective in preventing bone loss in postmenopausal women, its effectiveness in post-transplant setting remains uncertain. One report noted that intranasal salmon calcitonin 200 IU every other day can prevent early bone loss as effectively as alendronate and alfacalcidol[57]. But other studies failed to demonstrate its superiority to calcium supplementation in transplant recipients[58,59].

Teriparatide and denosumab

Recombinant human PTH teriparatide can improve BMD in patients with glucocorticoid-induced and postmenopausal osteoporosis[60,61]. A recent study of 26 kidney transplant recipients with daily teriparatide injection 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[62]. Denosumab, a monoclonal antibody against the receptor activator of nuclear factor kB ligand (RANKL), inhibits the development and activity of osteoclasts, and decreases bone resorption. Denosumab given subcutaneously twice yearly was shown to significantly increase BMD and decrease the risk of vertebral, nonvertebral and hip fractures in women with osteoporosis[63]. To our knowledge, its usage in kidney transplant patients has not been reported yet.

CONCLUSION

The bone diseases after kidney transplant have a complex pathophysiology and various histologies. The clinical management is challenging and needs to be individualized by assessing the risk factors in each patient and creating a plan for long-term care. Bone biopsy is the best way to define the type of disease process and to guide our clinical management. It is recommended that a baseline BMD should be documented before kidney transplant, with the BMD being followed intermittently[10,27]. All patients should be screened and treated for vitamin D deficiency, and they should receive counseling regarding smoking cessation, limiting alcohol intake, increasing mobilization and fall prevention.

For patients with baseline BMD consistent with osteopenia or osteoporosis, calcium and vitamin D supplements need be started and hypogonadism should be treated if HRT is not contraindicated. Bisphosphonate may be used for patients with osteoporosis, history of fracture 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 patients. If BMD is declining despite these therapies, then bisphosphonate or calcitonin may be considered. Persistent HPT should be treated with cinacalcet or parathyroidectomy. Other measures include: lowering the dosages of or discontinuing steroids if possible, correcting metabolic acidosis, hypophosphatemia, hypocalcaemia and malnutrition. With a failing renal allograft, patients should be managed in the same manner as CKD patient for recurring mineral and bone disorders.

It is important to note that despite the successful prevention and treatment of bone loss in transplant patients with several different types of medications, this effect has not resulted in a significant reduction in bone fracture yet. It is not clear whether the novel agent denosumab and/or teriparatide can be safely used in this population. More studies with the goal to restore the normal bone remodeling and to improve bone quality and strength are needed, so that the high incidence of facture can be successfully decreased in kidney transplant recipients.

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