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REVIEW

Osteoporosis in the adult solid organ transplant population: underlying mechanisms and available treatment options

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Abstract The prevention and treatment of osteoporosis is an increasingly important topic in the solid organ transplant (SOT) population. Compared to the general population, these patients are at an elevated risk of developing osteoporosis due to progressive disease, lifelong immunosuppressant therapy, and malnutrition. As patients live longer after transplant, chronic disease management is increasingly more important. Supplementation with calcium and vitamin D is often necessary in the SOT population due to a high incidence of vitamin D deficiency. Bisphosphonate therapy is most commonly used for prevention and treatment of osteoporosis, but therapy can be limited by renal dysfunction which is common in transplant recipients. Alternative agents such as teriparatide and calcitonin have not been shown to provide a significant impact on the rate of fractures in this population. Additionally, denosumab may be a promising treatment option due to its novel mechanism of action, and is currently being studied in renal transplant patients. Timely initiation of supplementation and treatment, and minimizing glucocorticoid exposure prior to and after transplantation will aid in the prevention and proper management of osteoporosis in these patients.

Keywords Bisphosphonates · Calcineurin inhibitors · Glucocorticoids · Immunosuppression · Osteoporosis · Transplant

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Introduction

Solid organ transplantation has progressed tremendously since the 1950s and is now considered a viable treatment option for many end organ disease states. Advances in surgical techniques and pharmacologic treatment have dramatically improved 1-year graft survival to greater than 80 % across many transplant types [1]. As patients live longer after transplantation, the adverse effects of lifelong immunosuppression are becoming more apparent. Transplant-associated osteoporosis is one complication that has increased concomitantly with the increase in post-transplant life expectancy. In fact, the risk of osteoporosis in the solid organ transplant (SOT) population has been shown to be greater than five times that of the general population [2]. Although the highest rate of bone loss is seen within the first year following transplantation, the burden of this disease has become more apparent as patients age and their cumulative exposure to immunosuppressant therapy increases [3, 4]. With this increasing burden comes a demand for therapy to prevent and treat this debilitating disease. This review will investigate the pathogenesis of osteoporosis in the adult solid organ transplantation population and discuss the current and potential treatment options.

Pre-transplant risk factors

Often, patients who present for transplant workup have some degree of baseline osteoporosis or osteopenia due to the pathophysiology of their chronic disease process. In postmenopausal women and men 50 years of age and older, osteoporosis is defined as a T-score of ≤−2.5, and low bone mass, or osteopenia, is defined as a T-score between −1.0 and −2.5 measured at the femoral neck with dual-energy X-ray absorptiometry (DXA). For premenopausal women, men less than

50 years old, and children, Z-scores are used to define osteoporosis, where a Z-score of ≤−2 is described as below the expected range for age, and a Z-score >−2 as within the expected range for age [5]. Abnormal bone formation and resorption markers have been observed in patients suffering from end-stage liver disease, and consequently, osteopenia or osteoporosis has been reported in up to 73 % of liver transplant candidates [4, 6]. Altered bone metabolism in patients with chronic kidney disease (CKD) is complex and can be attributed to altered hormonal levels, including parathyroid hormone (PTH), electrolyte abnormalities, including hyperphosphatemia and hypocalcemia, as well as vitamin D deficiency and an increase in pro-inflammatory markers. These dynamic processes result in alterations of bone resorption and turnover rates to varying degrees, placing dialysis patients at an increased risk for developing fractures (Fig. 1) [7]. The risk factors that predispose heart and lung transplant patients to osteoporosis are associated with the pathophysiology and treatment of congestive heart failure (CHF) and cystic fibrosis (CF), respectively. Both populations may suffer from hypogonadism, while CF patients likely have impaired calcium and vitamin D absorption. These factors contribute significantly to the osteopenia or osteoporosis that has been reported in as many as 66 % of lung transplant candidates and 31 % of heart transplant candidates [4, 8].

In addition to pathophysiologic changes that occur in patients with end-stage organ diseases, lifestyle and pharmacologic risk factors are also present prior to transplant, contributing substantially to the risk of osteoporosis. Exposure to both alcohol and nicotine are two important risk factors for osteoporosis largely present in the liver and lung transplant populations. Additional risk factors that exist for these populations include malnutrition and vitamin D deficiency, as well as low body weight and extensive corticosteroid exposure, especially in lung transplant candidates. Kidney transplant patients may also be exposed to calcineurin inhibitors for management of primary kidney disease such as glomerulonephritis prior to transplant, contributing to their osteoporosis risk. Transplant candidates as a whole are likely to be of older age, postmenopausal, suffer from some degree of immobility and malnutrition, and have kidney dysfunction as a result of other organ dysfunction (i.e., hepatorenal syndrome, congestive heart failure). All of these factors put these patients at risk for osteoporosis prior to transplant and contribute to their risk of developing osteoporosis post-transplantation as well [4, 8].

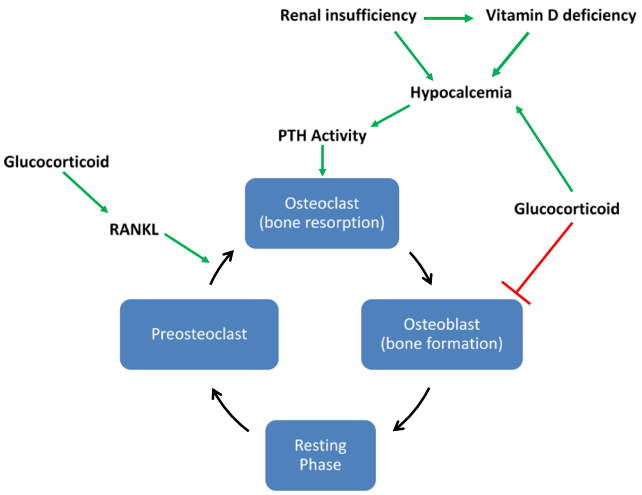

Fig. 1 Risk factors and bone formation. Illustrates the bone metabolism cycle and the relationship with risk factors for osteoporosis present in the solid organ transplant population. *PTH* parathyroid, *RANKL* receptor activator of nuclear factor-κB ligand; *green arrows* represent increased effect/activity and *red* represent decreased effect/activity

Post-transplant risk factors

Regardless of which organ-specific factors are present prior to transplant, the SOT population as a whole is at an elevated risk for developing osteoporosis post-transplantation due to both non-pharmacologic and pharmacologic reasons. Postoperatively, patients may be recovering in the hospital for weeks to months and therefore immobile for an extended period of time. Consequences of the surgery itself can result in acute or chronic renal dysfunction, contributing to the risk of osteoporosis due to altering the dynamic PTH, vitamin D, and calcium equilibrium. With decreased kidney function, hypocalcemia can occur as a result of phosphate retention and calcium-phosphate precipitate formation as well as poor conversion of vitamin D to its active form, 1,25-OH_2-D. Hypocalcemia leads to an increase in PTH secretion causing an increase in osteoclast activity and bone resorption in an effort to increase serum calcium levels.

Immunosuppressant agents, particularly glucocorticoids and calcineurin inhibitors, play a dominant role in the development of post-transplant osteoporosis. Treatment is recommended for the prevention of osteoporosis in patients of any age who have at least 3 months of anticipated steroid use at a daily dose of prednisone 5 mg or higher [5, 9]. Transplant recipients are specifically at an increased risk within the first 6 months post-transplant, when steroid doses are typically the highest. Glucocorticoids induce bone disease directly by decreasing osteoblast production, inducing osteoblast apoptosis, and promoting osteoclastogenesis through the receptor activator of nuclear factor-κB ligand (RANKL) system, resulting in reduced bone formation and accelerated bone breakdown. In addition, indirect effects of glucocorticoids including decreased intestinal calcium absorption and increased renal wasting, as well as reduced gonadal function contribute to the acute bone loss seen with high steroid use [3, 4]. The calcineurin inhibitors cyclosporine and tacrolimus are the cornerstone of immunosuppression in SOT recipients and have likewise been associated with bone loss. Rat models have demonstrated an increase in bone loss with these agents,

especially cyclosporine, caused by high-turnover osteoporosis. The true impact of these agents on human bone formation has been difficult to ascertain due to the fact that these medications are most commonly used in combination with glucocorticoids [3, 4]. In addition to a potential direct effect on bone metabolism, nephrotoxicity caused by calcineurin inhibitors can indirectly potentiate a patient's osteoporosis risk by causing secondary hyperparathyroidism. Because of the high risk transplant patients are at for bone loss, routine bone mineral density (BMD) monitoring is recommended for each group of patients depending on the transplant type (Table 1).

Treatment

Treatment guidelines specific to transplant recipients based on organ type address osteoporosis and provide recommendations for each patient population. The summary of these guidelines are shown in Table 2. As a whole, the guidelines recommend supplementation with calcium (1000–1200 mg/day) to achieve the recommended daily intake and vitamin D (400–1000 IU/day) as necessary to maintain serum hydroxyvitamin D >30 ng/mL. The International Society for Heart and Lung Transplantation (ISHLT) guidelines provide the most aggressive recommendation surrounding antiresorptive therapy in recommending its use in all heart transplant patients for at least 1 year post-transplant [10]. The American Association for the Study of Liver Diseases (AASLD) guidelines reserve the recommendation to start bisphosphonates for patients with osteoporosis or osteopenia, as evidenced by T-score ≤−2.5 or T-score between −1.5 and −2.5 with other risk factors [11]. The Kidney Disease Improving Global Outcomes (KDIGO) and the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) have more complex recommendations due to the fact that BMD does not predict the type of bone disease present post-kidney transplant, nor does it accurately predict the fracture risk in patients with stages 4–5 CKD compared to the general population. Only patients with GFR >30 mL/min/1.73 m^2 and T-score consistent with osteopenia or osteoporosis are recommended to consider using bisphosphonates within the first year post-transplant [12, 13]. This recommendation is most rigorous in the kidney transplant population because patients with CKD are at an elevated risk of fractures due to low bone mineral density on top of an underlying metabolic bone disease that may be present. These patients may have a high bone turnover bone disease due to secondary hyperparathyroidism, or a low bone turnover, adynamic, bone disease. Measurement of serum PTH and alkaline phosphatase can help to distinguish whether a high or low bone turnover disease is present, but bone biopsy is currently the best way to make this distinction and therefore remains the gold standard for diagnosis. Because bone biopsies are rarely conducted in clinical practice, bisphosphonates are not currently recommended for use in patients with GFR <30 mL/min/1.73 m^2 due to the risk of initiating treatment in a patient with

Table 1 Bone mineral density (BMD) screening guidelines

	Pre-transplantation	Post-transplantation
ISHLT [10]	DXA of lumbar spine and femoral neck	DXA of proximal femur and lumbar spine 1 year post-transplant
	Reasonable to perform spine radiographs to detect existing fractures	Annual DXA scans in patients receiving corticosteroids and/or bisphosphonate therapy
		Normal BMD: Repeat DXA in 3 years
		Osteopenia: Repeat DXA in 2 years
		Perform bone radiographs if any clinical suggestion of fracture
AASLD [11]	No specific screening recommendations	Normal BMD: DXA every 2–3 years for the first 5 years
		Osteopenia: DXA annually for the first 5 years
		Assess for risk factors[a] if osteopenia/osteoporosis is confirmed or atraumatic factors are present.
		Screening beyond 5 years depends on BMD progression and the presence of risk factors
KDIGO [12]	No specific screening recommendations	Measure BMD in patients with eGFR >30 mL/min/1.73 m^2 within first 3 months post-transplant if they receive corticosteroids or have risk factors[a] for osteoporosis
		Patients with stage 4–5 T CKD, routine BMD testing is not recommended
		Reasonable to consider a bone biopsy to guide treatment, specifically before the use of bisphosphonate

ISHLT International Society for Heart and Lung Transplantation, *AASLD* American Association for the Study of Liver Diseases, *KDIGO* Kidney Disease Improving Global Outcomes, *DXA* dual-energy x-ray absorptiometry

[a] Risk factors include calcium intake, 25(OH)D levels, gonadal function, thyroid function, concomitant medications, and thoracolumbar radiography

Table 2 Solid organ transplant osteoporosis treatment recommendations

	Daily supplementation	Anti-resorptive therapy	Considerations
ISHLT [10]	Calcium 1000–1200 mg[b] Vitamin D[a] 400–1000 IU	All heart transplant patients through the first year	Active vitamin D metabolites not considered first line May discontinue anti-resorptive therapy if steroids have been discontinued and T-score >1.5
AASLD [11]	Calcium 1000–1200 mg Vitamin D[a] 400–1000 IU	Consider if: T-score ≤−2.5 or history of fracture OR T-score −1.5 and −2.5 and other risk factors present	Recommended anti-resorptive therapy is alendronate 70 mg po weekly Other oral agents may be as efficacious IV zoledronic acid or ibandronate if cannot tolerate po Hormone replacement therapy is an alternative for postmenopausal women
KDIGO [12]	Vitamin D[a] 400–1000 IU	Consider within first 12 months if eGFR >30 mL/min/1.73 m^2 and low BMD	May consider bone marrow biopsy prior to bisphosphonate use due to concern for adynamic bone disease Frequently monitor calcium, phosphorus, PTH, alkaline phosphatases, and 25(OH)D Monitor serum calcium and phosphorus at least weekly until stable immediately post-transplant

ISHLT International Society for Heart and Lung Transplantation, *AASLD* American Association for the Study of Liver Diseases, *KDIGO* Kidney Disease Improving Global Outcomes

[a] As necessary to maintain serum 25-hydroxyvitamin D levels >30 ng/mL

[b] Guidelines last updated in 2010, since update the recommendation for the general public for calcium supplementation is a dose of 1000–1200 mg po daily. The guidelines recommend for patients to receive the recommended daily allowance

adynamic bone disease. Initiating anti-resorptive therapy in a patient with adynamic bone disease would only further decrease the rate of bone turnover and potentiate the risk of fracture [14–16].

Calcium and vitamin D

Inadequate vitamin D stores are prevalent among candidates on the transplant waiting lists of all organ types, with insufficiency reported in up to 91 % of patients and deficiency in 55 % of patients. Furthermore, insufficiency has been reported in up to 97 % of patients, and severe deficiency in up to 33 % of patients post-transplantation [17]. Risk factors for vitamin D deficiency in this population include decreased vitamin D intake due to poor nutrition after transplant, decreased sun exposure due to increased risk of skin cancer with immunosuppression, hepatic dysfunction, renal dysfunction, and glucocorticoid use which can increase catabolism of 25(OH)D [3, 17]. Supplemental vitamin D is recommended for all solid organ transplant recipients with deficiency in an effort to reduce osteoporosis risk. Vitamin D supplementation counteracts the deleterious effects of glucocorticoids by promoting intestinal calcium absorption, reducing secondary hyperparathyroidism, and promoting osteoblast differentiation. Notably, the immune-modulating effects of vitamin D provide benefit beyond that of osteoporosis protection by contributing to graft survival and increasing time to rejection. Insufficient vitamin D levels have been associated with increased episodes of rejection in liver, kidney, and lung transplant patients at 8 months, 10 years, and 1 year post-transplantation, respectively [18–20]. Due to the vast amount of vitamin D insufficiency in this population and the numerous benefits seen with normal serum levels, all transplant recipients should maintain serum 25(OH)D >30 ng/mL. Either ergocalciferol or cholecalciferol is appropriate for supplementation. Typically, patients require daily doses of 400–1000 IU of cholecalciferol in order to achieve normal levels which can be easily obtained without a prescription. When treating vitamin D deficiency, however, prescription strength ergocalciferol 50,000 IU dosed once weekly until 25(OH) D levels are approximately 30 ng/mL is recommended and is a convenient, once weekly dosing schedule. Treatment should continue for 8–12 weeks at which point maintenance therapy with daily cholecalciferol can resume [5]. The vitamin D analogue calcitriol is not recommended as first line therapy due to the risks of hypercalcemia and hypercalcuria, and subsequently the frequent urinary and serum monitoring that is required [10–13, 17]. Calcium supplementation is also recommended to optimize bone remodeling and mineralization at a dose of 1000–1200 mg divided daily, with a maximum of 500 mg elemental calcium per dose due to absorption limitations. Patients' serum calcium, phosphorus, and PTH levels should be routinely monitored as well as signs and symptoms of nephrolithiasis, especially in those with renal dysfunction. Many combination calcium and vitamin D products are available over the counter, which may be a

helpful treatment option in this population already bearing a prescription medication burden. Calcium citrate should be used in patients requiring acid suppressant therapy with proton pump inhibitors to provide adequate absorption.

Bisphosphonates

Robust literature supports the use of bisphosphonates because of their protective effects on bone mineral density (BMD) in the kidney, heart, and liver transplant populations. A summary of the data for both the prevention and treatment of osteoporosis and osteopenia with bisphosphonates in the SOT population is shown in Tables 3 and 4. Although this evidence demonstrates positive effects such as increasing BMD and decreasing the rate of loss of BMD seen after transplant, the beneficial effect on fracture rate is yet to be delineated [38]. Only two studies have demonstrated significant reductions in fracture risk. The first, conducted in liver transplant patients by Bodingbauer et al., used significantly higher zoledronic acid doses than that is currently recommended for osteoporosis treatment [34]. Additionally, Fahrleitner-Pammer et al. showed a significant decrease in the rate of fractures compared to supplementation alone with the use of IV ibandronate in heart transplant patients. The annual cumulative corticosteroid exposure in this study, however, was approximately 17 g which is much higher than an average of <10 g, which has been reported in other studies [24]. Adverse effects of bisphosphonates often reported in these studies include dyspepsia with oral agents, infusion reactions, and flu-like symptoms with parenteral agents, as well as hypocalcemia. The incidence of adverse events reported were generally not significantly greater in one treatment group versus another, even when compared to supplementation alone, indicating the relative safety of bisphosphonates.

Limitations to this therapy exist in this population most notably for the recommendation to avoid use in patients with renal dysfunction, Scr >2 mg/dL or CrCl <30–35 mL/min according to the package inserts [39–43]. These agents have not been studied extensively in patients with CrCl <30 mL/min, and with this level of kidney disease, patients may be suffering from low turnover bone and mineral disorder, in which case an anti-resorptive therapy would not be appropriate. A secondary analysis of patients with normal to severely impaired renal function in the fracture intervention trial (FIT) found that alendronate increased BMD regardless of CrCl, without significant differences in adverse events. Because bisphosphonates are renally excreted, using them in patients with decreased renal function can lead to potentiated electrolyte abnormalities including hypocalcemia, but may also lead to greater effects on BMD and fracture rates. This study found that patients with CrCl <45 mL/min had a greater increase in total hip BMD compared to those with CrCl >45 mL/min with a similar increase in spine BMD and fracture reduction [44]. Only 10 % of patients in this study had CrCl <45 mL/min, and an even smaller number of patients had CrCl <30 mL/min, therefore whether this data can be extrapolated to patients with stage 4 or 5 CKD is unclear. Other studies have found an association between prolonged bisphosphonate therapy with the development of adynamic bone disease in patients with stages 4–5 CKD [22].

In addition to the risk of developing adynamic bone disease, the use of IV bisphosphonate therapy has also been associated with a risk of renal injury, predominantly in the oncology population where high dose bisphosphonate therapy is routinely used. The mechanisms behind the cause of renal injury are not completely clear, but may be associated with high exposure after IV administration. Renal injury often manifests as a transient increase in Scr within 10 days after IV administration. Alternatively, patients may present with acute renal failure and tubular necrosis, a slow progressive rise in Scr, or rarely, focal segmental glomerulosclerosis. Renal injury has been more commonly reported with the use of IV pamidronate and zoledronic acid for the treatment of metastatic bone lesions than for osteoporosis. This is likely due to the higher and more frequent dosing schedule recommended for bone lesions; however, contribution from the underlying malignancy cannot be ignored, making the true risk from bisphosphonate therapy difficult to assess [45]. Nonetheless, based on the frequency of renal toxicity reported with both zoledronic acid and pamidronate in clinical trials and in case reports of patients with breast cancer, prostate cancer, and multiple myeloma, the package insert recommends long-term Scr monitoring and adjusted dosing strategies for these indications. The recommendation for zoledronic acid includes evaluating the patient's change in Scr prior to each dose administration and implementing a gradual dose reduction from the highest dose of 4 mg for patients with CrCl >60 mL/min to 3 mg for patients with CrCl = 30–39 mL/min. Zoledronic acid should be administered over at least 15 min due to higher increases in serum creatinine observed in clinical trials in patients who received zoledronic acid administered over only 5 min. An infusion time of 15 min is recommended in the current package labeling in addition to the adjusted dosing strategy based on CrCl. This dosing strategy was evaluated in a study in multiple myeloma patients by Berenson et al. who found that prolonging the infusion beyond 15 min did not have a significant impact on Scr over time. Interestingly, this study was conducted prior to the package label change; therefore, all patients in this study received 4 mg regardless of baseline renal function. Despite all patients receiving the 4 mg IV dose, there was not a protective effect on the rise in Scr at 12 or 24 months by prolonging the infusion to 30 min [46]. Of note, when treating hypercalcemia of malignancy, there is no dosage reduction recommended for patients with Scr <4.5 mg/dL, likely due to the risk-benefit ratio of using an IV

Table 3 Studies evaluating bisphosphonate prophylaxis in solid organ transplant patients

Study	Txp	Treatment (*N*)	Comparator (*N*)	Length of therapy (months)	Immunosuppression	Mean percent change in BMD (treatment vs comparator)	Fracture risk	Conclusion
Grotz et al. (2001) [21]	Kidney	IBA 1 mg IV at KT, 2 mg IV mos 3, 6, 9[a] (40)	Calcium >1000 mg/d (40)	12	CsA; GC; MMF Antithymocyte globulin for ULD	LS: −0.9+6.1 vs −6.5+5.4 % $p<0.0001$ FN: +0.5+5.2 vs −7.7+6.5 % $p<0.0001$ Incidence of spine deformities: 7 vs 23 $p=0.047$ Height loss: 0.5+1 vs 1.1+1 cm $p=0.049$	N/A	IBA significantly decreased the progression of osteoporosis indicated by loss in LS and FN BMD
Coco et al. (2003) [22]	Kidney	PAM 60 mg IV at KT, 30 mg IV at mos 1, 2, 3, 6[a] (31)	Calcitriol and calcium carbonate (28)	6 (PAM) 12 (COMP)	CsA or Tac; GC	LS: −0.63+0.03 vs −4.6+0.08 % $p<0.05$ at 6 months −0.39+0.05 vs. −5.81+0.09 % $p<0.01$ at 12 months H: NS at 12 months	N/A	PAM significantly decreased the reduction in vertebral BMD. Sustained for 6 mos afterward
Schwarz et al. (2004) [23]	Kidney	ZOL 4 mg IV Q 3 mos × 2[a] (9)	Calcium citrate 1000 mg/d (10)	3 (ZOL) 6 (COMP)	CsA; GC; MMF	LS and FN: NS at 3 years	N/A	ZOL for 3 mos post-KT did not lead to significantly greater BMD improvement 3 years post-KT
Fahrleitner-Pammer, A. et al. (2009) [24]	Heart	IBA 2 mg IV q 3 mos[a] (17)	Calcium + vitamin D (18)	12	CsA; GC; MMF	LS: unchanged vs −25 % ($p<0.0001$) FN: unchanged vs −23 % ($p<0.0001$)	Vertebral fracture: 13 vs 53 % $p=0.04$	IBA preserved LS and FN BMD. Significantly less vertebral fractures after 12 months
Shane, E. et al. (2012) [25]	Heart and Liver	ZOL 5 mg IV × 1[a,b] (37)	ALN 70 mg weekly[a,b] (35)	12	CsA or Tac; GC	All patients: LS: +2.0 % vs. unchanged $p=0.009$ Hip and femoral neck: NS Heart: LS: +1.6 vs −3 % ($p<0.001$) Liver: LS: +2.7 vs. +3.6 % (NS between groups)	N/A	ZOL significantly increased LS BMD in all patients and HT patients alone more than ALN at 12 mos post-HT. ALN significantly improved LS BMD in LT patients

ALN alendronate, *BPS* bisphosphonate, *COMP* comparator, *CsA* cyclosporine, *CTN* calcitonin, *ETD* etidronate, *FN* femoral neck, *F* femur, *GC* glucocorticoids, *HT* heart transplant, *H* hip, *IBN* ibandronate, *KT* kidney transplant, *LT* liver transplant, *LS* lumbar spine, *NS* no significant difference, *mg/d* mg per day, *Mos* months, *MMF* mycophenolate mofetil, *PAM* pamidronate, *RSN* risedronate, *Tac* tacrolimus, *Txp* transplant, *ULD* unrelated living donor, *ZOL* zoledronic acid

[a] Calcium + vitamin D daily, in trials where supplementation alone was the comparator, those in the treatment group received the same supplementation regimen as the control group

[b] All patients also received ergocalciferol 50,000 IU/d for 5 days prior to randomization

[c] Studies included if mean T-score <−1 or Z-score <−2 for treatment or control group at baseline

Table 4 Studies evaluating bisphosphonate treatment in solid organ transplant patients

Study	Txp	Treatment (*N*)	Comparator (*N*)	Length of therapy (months)	Immunosuppression	Mean percent change in BMD (treatment vs comparator)	Fracture risk	Conclusion
Nowacka-Cieciura E. et al. (2006) [26]	Kidney	ALN 10 mg/d or RSN 5 mg/d (39 total)	Placebo (27)	6 (12 if OP at 6)	CsA or Tac; GC; azathioprine or rapamycin	LS: +2.26 vs. −2.1 % at 12 mos T-score in BPS group: −2.22+1.06; −2.07+1.25; −1.89+1.07 at 1, 6, and 12 mos	N/A	BPS (ALN/RSN) significantly increased T-score and LS BMD from 6-12 mos post-KT
Torregrosa, J.V. (2007) [27]	Kidney	RIS 35 mg weekly[a] (39)	Calcium carbonate 2500 mg/d + cholecalciferol 800 IU/d (45)	12–36 mos after KT for 12 mos	CsA or Tac; GC; + MMF	T-score at LS and FN: LS: NS at 6 mos; RIS lower than COMP at 12 mos ($p<0.05$) FN: NS at 6 or 12 mos Bone pain: 3 vs 18 % at 12 mos $p<0.05$	NS	RIS significantly reduced BM loss and bone pain without significant side effects
Omidvar et al. (2011) [28]	Kidney	PAM 90 mg IV monthly x 3[a] (20)	ALN 70 mg weekly[a] (20)	3 weeks after KT for 3 mos	CsA, GC, MMF	FN: −1.42 and −2.03 % ($p=0.003$) F: −1.40 and −1.42 % ($p=0.03$) LS: NS	N/A	PAM significantly decreased the reduction in F and FN BMD at 6 mos, compared to ALN
Torregrosa, J. V. (2011) [29]	Kidney	PAM 30 mg IV Q 3 mos × 2[a] (24)	Calcium 1000 mg/d + cholecalciferol 800 IU/d (15)	PAM: 3 COMP: 12	CsA; GC; MMF	LS: +1 vs −6 % at baseline ($p<0.05$) FN and F: NS	NS	PAM significantly improved LS BMD at 12 mos post-KT, but had no significant impact on fracture risk
Gilfraguas, L. et al. (2012) [30]	Heart	CTN nasal spray 200 IU/d[a] (42) OR ETD 400 mg/d x 14d Q3 mos[a] (33) OR ALN 10 mg/d[a] (45)	Calcium 1000 mg/d + vitamin D3 800 IU/d (102)	2 years	CsA; GC	LS: −0.93 % (CTN), −1.87 % (ETD), +4.9 % (ALN, $p<0.001$), −3.07 % (COMP) F: −3.6 % (CAL), −4.6 % (ETD), −0.5 % (ALN, $p<0.001$), −3.2 % (COMP)	NS	ALN preserved LS BMD and led to a significantly lower reduction in F BMD after 2 years of treatment. No significant impact on fracture risk
Millonig, G. et al. (2005) [31]	Liver	ALN 70 mg weekly[a] (98)	Calcium 1000 mg/d + vitamin D 400 IU/d (38)	ALN: 48 COMP: while listed	CsA or Tac; GC	ALN: Significant improvement in lumbar spine (4 to 12 mos post-LT) and trochanter (4 to 12 mos and 24 to 36 mos post-LT)	N/A	ALN prevented bone loss in patients with OP and osteopenia, and increased BMD in patients with OP
Atamaz, F. et al. (2006) [32]	Liver	ALN 70 mg weekly (44)	Calcium 1000 mg/d + calcitriol 0.5 mcg/d (48)	2 years	CsA or Tac; GC	LS: 5.1+3.9 vs 0.4+4.2 %, (12 mos, $p<0.05$); 8.9+5.7 vs 1.4+4.9 % (24 mos, $p<0.05$) FN: 4.3+3.8 vs −1.1±3.1 % (12 mos, $p<0.05$); 8.7+4.8 vs 0.6+4.5 %, (24 mos, $p<0.05$) Hip: 3.6+3.8 vs −0.6+4.0 % (12 mos, $p<0.05$); 6.2+3.8 vs 0.3+4.6 % (24 mos, $p<0.05$)	NS	ALN significantly improved BMD at LS and prevented reduction in hip BMD

Table 4 (continued)

Study	Txp	Treatment (*N*)	Comparator (*N*)	Length of therapy (months)	Immunosuppression	Mean percent change in BMD (treatment vs comparator)	Fracture risk	Conclusion
Crawford, B.A.L. et al. (2006) [33]	Liver	ZOL acid 4 mg IV at LT and months 1, 3, 6, 9[a] (32)	Calcium carbonate 600 mg/d + ergocalciferol 1000 IU/d (30)	12	CsA or Tac; azathioprine or MMF; GC	Percent change treatment-control at 3, 6, 12 mos: LS: 4 % (p=0.009), 4.2 % (p=0.015), NS FN: 4.7 % (p=0.002), 4.6 % (p=0.002), NS Hip: 3.8 % (p<0.001), 5.1 % (p<0.001), 2.4 % (p=0.048)	NS	ZOL significantly improved BMD at the spine at 6 mos and at the hip at 12 mos after LT. Treatment led to significantly greater incidences of hypocalcemia (13 vs 3)
Bodingbauer M., et al. (2007) [34]	Liver	ZOL 4 mg IV monthly x 6 then Q 3 months × 2 (8 total doses)[a] (47)	Calcium carbonate 1000 mg/d + vitamin D3 800 IU/d (49)	12	Thymoglobulin induction; CsA or Tac, GC	No significant difference in BMD_L at 6 or 12 months	4 (8.5 %) vs. 11 (22.5 %) p=0.05 Fracture + death: 26 vs. 46 % p=0.047	High dose ZOL significantly decreased the frequency of vertebral fractures at 24 mos BMD did not correlate to fracture rate
Monegal, A. et al. (2009) [35]	Liver	PAM 90 mg IV Q 3 months × 2[a](38)	Calcium 1000 mg/d + vitamin D 16,000 IU q 15 days (41)	PAM: 3 COMP: 12	CsA; GC; MMF	LS: +2.9 vs. +1 % p<0.05 at 12 mos Trochanter: −0.7 vs. −3.7 % p<0.05 (at 6 mos) NS at 12 mos	NS	PAM significantly increased LS BMD at 12 mos and trochanter BMD at 6 mos post-LT
Guadalix, S. (2011) [36]	Liver	RIS 35 mg weekly[a] (45)	Calcium 1000 mg/d + vitamin D3 800 IU/d (44)	12	Tac; GC; + MMF; + CsA At 6 mos, 80 % pts steroid-free	LS: increase with RIS vs baseline (p=0.0014) at 6 mos; increase with RIS and COMP groups vs baseline at 12 mos (p=0.001) FN: NS	NS	LS BMD improved significantly in both groups. 12 mos of RIS did not increase LS BMD more than supplementation
Kaemmerer, D. et al. (2012) [37]	Liver	IBA 150 mg po monthly + calcium 1000 mg/d + vitamin D3 800 IU/d (74)	–	24	Tac; GC; MMF; basaliximab	Compared to baseline: LS: 1.05+0.21 (12 mos, p=0.001), 1.11+0.19 (24 mos, p=0.001) vs 0.98+0.19 FN: 0.88+0.16 (12 mos, p=0.002) and 0.90+0.15 (24 mos, p=0.001) vs 0.86+0.14	N/A	IBA significantly increased LS and FN BMD with treatment for 24 mos post-LT

Studies included if mean T-score <−1 or Z-score <−2 for treatment or control group at baseline

All patients also received ergocalciferol 50,000 IU/day for 5 days prior to randomization; *ALN* alendronate, *BPS* bisphosphonate, *COMP* comparator, *CsA* cyclosporine, *CTN* calcitonin, *ETD* etidronate, *FN* femoral neck, *F* femur, *GC* glucocorticoids, *HT* heart transplant, *H* hip, *IBN* ibandronate, *KT* kidney transplant, *LT* liver transplant, *LS* lumbar spine, *NS* no significant difference, *mg/d* mg per day, *Mos* months, *MMF* mycophenolate mofetil, *PAM* pamidronate, *RSN* risedronate, *Tac* tacrolimus, *Txp* transplant, *ULD* unrelated living donor, *ZOL* zoledronic acid

[a] Calcium + vitamin D daily, in trials where supplementation alone was the comparator, those in the treatment group received the same supplementation regimen as the control group

bisphosphonate in this setting [43, 47]. Pamidronate should be administered at an even slower rate of 2 h and delivered in a larger volume of 250 mL compared to 100 mL required for zoledronic acid, in an effort to reduce renal injury. According to the package insert, pamidronate may be used in patients with CrCl <30 mL/min at a prolonged infusion rate of 3–4 h, and a dose reduction may also be considered [47]. Pamidronate is not currently approved for the prevention or treatment of osteoporosis, but has been studied for this purpose in transplant patients. These studies typically excluded patients with CrCl <30 mL/min; consequently, it is unknown what the approved dosing recommendation will be for osteoporosis treatment in patients with renal dysfunction.

Often, patients suffer from some degree of renal deficiency post-transplantation which may arise immediately or develop over time, due in part to chronic use of calcineurin inhibitors. Since the rate of bone loss, and consequently the risk of fractures, is the highest in the first 6–12 months after transplant, this is the time that anti-resorptive therapy can have the greatest benefit. When considering the use of bisphosphonates in patients with CrCl <30 mL/min, the risks of developing low bone turnover disease must be weighed against the benefit of preserving bone mineral density. This risk-benefit comparison will be different depending on the specific patient population being considered. Kidney transplant patients who have suffered from ESRD for an extended period of time prior to transplant and continue to have renal dysfunction post-transplantation are at a higher risk of having an underlying metabolic bone disease. Consequently, the risks of bisphosphonate therapy may not outweigh the benefits and it may be best to avoid these agents altogether for this particular population. Furthermore, kidney transplant patients develop low bone turnover over time so it may be more prudent to use bisphosphonates solely for osteoporosis treatment rather than prophylactically [22]. Whether adynamic bone disease as a result of bisphosphonate therapy correlates to a fracture risk in this population has yet to be demonstrated; however, this provides another reason to exercise caution when using bisphosphonates in kidney transplant patients. In transplant recipients who have developed kidney dysfunction acutely after transplant and have a T-score consistent with osteopenia or osteoporosis, the benefit of bisphosphonate treatment on BMD likely outweighs the risk of developing adynamic bone disease, at least in the first 12 months post-transplantation. If bisphosphonate therapy is used in a patient with CrCl <30 mL/min, it may be reasonable to use a one-time dose of 3 mg of zoledronic acid, or pamidronate administered over a prolonged infusion time with the consideration of decreasing the dose as well to reduce the risk of hypocalcemia, which is used in patients with this degree of renal dysfunction in the oncology population.

The sustained duration of action of bisphosphonates combined with the risks associated with prolonged use including atypical fractures and osteonecrosis of the jaw has led to investigation into optimal treatment duration with these agents. The fracture intervention trial long-term extension (FLEX) was an extension of the FIT trial, and showed that 10 years of treatment with alendronate led to significantly higher total hip and spine BMD as well as a significant reduction in clinically recognized vertebral fractures compared to ceasing treatment after 5 years in postmenopausal women. Although those who stopped treatment after 5 years still had mean hip and spine BMD at or above pretreatment levels determined 10 years prior, and there was no significant difference in the cumulative risk of nonvertebral fractures between the groups. Notably, no cases of osteonecrosis of the jaw were reported in either group, nor was there a significant difference in adverse events between the groups [48]. This study implies that 5 years of bisphosphonate therapy has some residual effects and that extended use beyond 5 years may not provide additional significant benefit on the rate of fractures other than for clinical vertebral fractures. However, the increase in BMD demonstrated with extended use in the study as well as the lack of significant difference in adverse events indicates that extended therapy may be considered in patients with an elevated fracture risk. Current osteoporosis guidelines for postmenopausal women recommend 10 year treatment duration followed by a drug holiday for 1–2 years for high-risk patients [49]. Furthermore, a study by Schwarz et al. investigated the long-term impact of zoledronic acid administered 2 weeks and 3 months after kidney transplantation and found a significant improvement in lumbar spine and femoral neck BMD in the treatment group compared to placebo when measured at 6 months post-transplantation. This significant increase in lumbar spine BMD, however, was not sustained at 3 years. An initial significant response was seen with zoledronic acid therapy, indicating that prolonged treatment may have led to a sustained impact on BMD [23]. Given the number of risk factors predisposing solid organ transplant recipients to osteoporosis, an extended course of 10 years of treatment may be reasonable, although studies investigating extended treatment duration in this population have yet to be conducted.

Teriparatide

The once-daily subcutaneous recombinant human parathyroid hormone (PTH) injection, teriparatide, stimulates osteoblast activity preferentially over osteoclast activity, resulting in new trabecular and cortical bone formation. Physiologically, teriparatide has the same effects on the kidneys and bones as PTH, resulting in increased renal production of 1,25-dihydroxyvitamin D3, intestinal absorption of calcium, and an increased rate of release of calcium from bone into the blood. Because teriparatide is administered at small daily doses of 20 mcg, an anabolic effect is seen, resulting in bone

formation. Due to its mechanism of action, teriparatide should be discontinued after 24 months. At this time, the anabolic effects of teriparatide decline and patients should be transitioned to anti-resorptive therapy [50]. Teriparatide has been shown to increase BMD significantly greater than alendronate and result in fewer vertebral fractures in patients with glucocorticoid-induced osteoporosis; however, this effect has not been demonstrated in the solid organ transplant population [51]. When compared to 1200 mg calcium and 800 IU cholecalciferol daily in kidney transplant patients, femoral neck BMD remained stable, but there was no improvement in lumbar spine BMD. This study was actually stopped early because of a greater improvement in lumbar spine BMD that was seen in the placebo group. No significant adverse effects were reported in the study [52]. Due to the nature of the medication, no renal dose adjustment is required; however, the daily subcutaneous injection may be cumbersome for some patients. In addition, this medication requires a Risk Evaluation and Mitigation Strategy (REMS) to ensure that healthcare providers are aware of the 24-month maximum duration and patients are aware of the increased risk of osteosarcoma seen in rat studies. This medication should therefore be avoided in patients at risk of developing osteosarcoma (i.e., those with Paget's or other bone disease, prior radiation therapy, open epiphyses). Other common side effects of the medication include angina, hypotension, hyperuricemia, and hypercalcemia.

Calcitonin

Intranasal calcitonin has been studied in kidney transplant patients after showing success in improving lumbar BMD in both postmenopausal women and men suffering from idiopathic osteoporosis. The data that exists in the solid organ transplant population is also promising, although no data demonstrates a significant effect on fracture prevention in any population. Daily intranasal calcitonin improved BMD in kidney transplant patients with baseline osteoporosis, demonstrated by improvement in DXA T-score evaluated 3 months after baseline T-score of <−2.5 [53]. Furthermore, a study in cardiac transplant patients demonstrated a protective effect on BMD within the first year post-transplant when compared to calcium and vitamin D alone. This study followed patients for >7 years post-transplant, but did not find a significant difference in BMD after the first year [54]. Compared to pamidronate, a significantly higher BMD was seen with pamidronate treatment. Although pamidronate showed a greater protective effect on BMD than calcitonin did initially after transplantation, this effect was no longer significant 18 months after transplantation, verifying the point that bone loss is most significant within the first year [55]. This data suggests that calcitonin may be considered as an adjunctive therapy to calcium and vitamin D in patients who may not be able to tolerate bisphosphonate therapy. Although no significant adverse effects were reported in these studies, hypocalcemia is a potential side effect of calcitonin therapy and an increased risk of malignancies has also been reported with the nasal formulation [56]. These studies are limited by their small sample sizes, so larger studies in other organ transplant groups need to be conducted in order to better distinguish the role of calcitonin in osteoporosis prevention and treatment.

Denosumab

Little data exists examining the use of denosumab in the solid organ transplant population. Its use in postmenopausal women has shown a reduction in hip and nonvertebral fractures as well as changes in BMD and bone turnover markers [57, 58]. Its unique mechanism as a RANKL inhibitor prevents the formation, function, and survival of osteoclasts, resulting in decreased bone resorption and increased bone mass and strength [59]. An increase in osteoclast activity contributes to the mechanism of post-transplant bone loss due to the effects of calcineurin inhibitors on osteoclast activity and glucocorticoid activation of the RANKL pathway. Denosumab has also been studied in rheumatoid arthritis patients treated concurrently with glucocorticoids, at an average daily prednisone dose of 4–5 mg (range 1–15 mg). This study showed a significant increase in spine, hip, and femoral neck BMD at 12 months follow up compared to placebo regardless of concurrent steroid therapy as well as a decrease in bone turnover markers [60]. Approximately 20 % of patients in this study receiving denosumab were also being treated with bisphosphonates; therefore, the effects of denosumab monotherapy in patients on chronic steroid therapy need to be further investigated. Theoretically, denosumab could play a major role in the transplant population due to its mechanism of action in addition to the fact that it does not need to be dose adjusted for renal function, has no known drug interactions, and is a subcutaneous injection administered every 6 months. Possible side effects include hypocalcemia, hypophosphatemia, arthralgia, and aseptic necrosis of the jaw. In addition, serious infections leading to hospitalization were reported more frequently in a clinical trial in patients treated with denosumab compared to placebo. Although the overall incidence of infections between the two groups was similar, clinicians should be aware of this safety risk in immunocompromised patients. Currently, there is an ongoing clinical trial investigating its use in kidney transplant patients which could potentially impact the future of osteoporosis therapy in the transplant population [61].

Bone turnover markers

Monitoring markers of bone turnover including serum procollagen type 1 *N*-propeptide (PINP) and C-terminal telopeptide of type 1 collagen (CTX), which are markers for bone formation and resorption respectively, may be an alternative tool to BMD to assess treatment response. These markers have been recommended by the International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine to be used as references in assessing bone turnover in clinical trials. Evaluating individual patient response rather than a large group response is currently more valuable due to wide inter-patient variability. The within-patient variability is less, although still present, and should be taken into account when evaluating treatment response. Baseline levels should always be drawn in order to make a meaningful assessment. Monitoring these markers has limitations in that there are currently no reference standards, there are both inter-patient and within-patient variability that must be accounted for, BTM levels are impacted by a number of factors (e.g., age, gender, renal impairment, medications), and their ability to predict fracture risk is still unclear. Typically, studies that have reported impacts on fracture rate have used inconsistent statistical analyses to evaluate the association between fracture rates and changes in BTM. One large advantage with BTM monitoring is that changes can be seen more quickly than changes in BMD. Bisphosphonate therapy, for example, can lead to BTM changes in approximately 4 weeks, which can allow for early assessment of treatment response and adherence [62]. Continued research in this area is necessary to develop international research standards and better establish the relationship between BTM and fracture risk. The opportunity to use BTM to evaluate treatment response provides a possibility to better guide treatment decisions and duration of therapy especially in patients in whom BMD is a weaker predictor of fracture risk such as the transplant population

Hormone replacement therapy

Hormone replacement therapy is a treatment option for osteoporosis in patients with hypogonadism, but its use has not been thoroughly investigated in the solid organ transplant population. Raloxifene treatment has been shown to increase BMD and reduce the risk of vertebral fractures in postmenopausal women with normal renal function (Scr <2.5 mg/dL) as well as improve lumbar spine BMD in postmenopausal women on hemodialysis [63, 64]. Despite this evidence in the postmenopausal population, these trials excluded patients treated with steroids, making it difficult to extrapolate this data to a population maintained on glucocorticoids for an extended period. In postmenopausal liver transplant patients, 2 years of treatment with transdermal estrogen beginning 6 months after transplant increased BMD in the lumbar spine and femoral neck, with the largest improvements seen within the first year [65]. Hypogonadism is also a concern in men post-transplant particularly within the first 6 months, when it is more common to see low serum testosterone levels. In one study investigating hormone replacement in hypogonadal heart transplant patients, there was no difference in BMD with the addition of calcitriol to calcium alone. This lack of difference was attributed to hormone supplementation for hypogonadal patients in both groups [66]. On the other hand, another study investigating alendronate and calcitriol in heart transplant patients did not find a correlation between testosterone levels and rates of bone loss [67]. This conflicting evidence indicates that there may not be a true advantage in using testosterone post-transplantation to aid in the prevention of osteoporosis when using another effective agent. Furthermore, estrogen replacement may only be beneficial in postmenopausal transplant patients until further studies indicate otherwise. Before hormone replacement therapy is recommended, the risks of breast cancer, endometrial cancer, venous thromboembolism, and stroke should be weighed against the potential benefits of therapy.

Alternative immunosuppressant regimens

Evidence behind the benefits of glucocorticoid-sparing regimens is controversial. In one longitudinal study of 57 simultaneous kidney-pancreas transplant recipients, no patients were found to have osteoporosis 4 years post-transplantation. Patients in this study were on triple immunosuppressant therapy, although 26 % of patients had steroid-free regimens at the end of the first year. All patients were concomitantly treated with vitamin D, calcium, and bisphosphonates as appropriate; however, the lack of prolonged steroid therapy likely played a large part in the improvement in T-score seen overtime [68]. Vincenti et al. found that an early steroid withdrawal regimen, ending steroids at day 7 post-transplant, led to a trend in improved lumbar spine and hip BMD at 1 year after kidney transplant, although this was not significant compared to patients receiving a standard steroid regimen [69]. With regard to preventing fractures, one study demonstrated a significant reduction in the composite endpoint of avascular necrosis and/or fractures measured at 5 years post-kidney transplant in patients whose immunosuppression regimen included only 7 days of steroid therapy compared to a standard steroid regimen. Individually, these outcomes were not significantly improved in the steroid withdrawal group, although there was a trend for decreased rates of both [70]. Alternatively, another study of kidney, pancreas, and liver transplant recipients that limited glucocorticoid therapy to 6 months post-transplantation found a fracture rate of 24–42 %,

Table 5 Cost comparison of osteoporosis treatment

Generic name	Brand name	Available generic	Dosing regimen	WAC Package Price [73]	Day Supply
Alendronate	Fosamax	Y	5 mg or 10 mg po daily 35 mg or 70 mg po weekly	$263.40 (daily dose) $12.78 (35 mg weekly) $16.02 (70 mg weekly)	90
Ibandronate	Boniva	Y	150 mg po monthy 3 mg IV Q 3 months	$416.18 (PO) $300.00 (IV)	90
Risedronate Risedronate DR	Actonel Atelvia	N	5 mg po daily 35 mg po weekly 35 mg DR po weekly 150 mg po monthly	$265.67 (daily dose) $209.21 (weekly dose) $232.46 (Atelvia DR) $223.80 (monthly dose)	30
Pamidronate	Aredia	N	30 or 90 mg IV monthly	$16.57 (30 mg vial) $36.96 (90 mg vial)	30
Zoledronic acid	Reclast	Y	5 mg IV yearly	$420.00	365
Teriparatide	Forteo	N	20 mcg subcutaneous daily	$2424.96	30
Calcitonin	Fortical	Y	200 IU intranasal daily	$89.84	30
Denosumab	Prolia	N	60 mg subcutaneous Q 6 months	$1109.70	180

which is similar to what has been previously reported with traditional immunosuppressant regimens [71]. Although these trials may not demonstrate convincing evidence that early steroid withdrawal is directly associated with improvements in BMD and fracture rates, it is important to note that these studies did not show significant differences in long-term graft function between those limited to 7 days of steroids compared to a standard steroid taper. Limiting steroid exposure in patients that are eligible for steroid-sparing regimens may not only lead to improvements in bone complications but also reduce insulin requirements, weight gain, and triglyceride levels without compromising graft survival.

In addition to limiting glucocorticoid use, consideration may be given to the inclusion of the mTOR inhibitors, sirolimus and everolimus, as part of maintenance immunosuppression. One trial investigating the effects of calcineurin inhibitors, mycophenolate mofetil, and sirolimus on osteoclast activation and function found that sirolimus inhibits osteoclast formation and therefore may have the ability to counteract the osteoclast promoting effects of glucocorticoids and calcineurin inhibitors [72]. The impact of sirolimus on osteoclast activity was determined using bone resorption biomarkers. Therefore, outcome data on BMD and fracture risk needs to be investigated before understanding the place for sirolimus and everolimus in the protection against osteoporosis.

Adherence

With the number of different treatment options available, cost and dosage formulations should also be considered. Table 5 provides a summary of the costs of current treatment regimens. Oral bisphosphonates are available in daily, weekly, or monthly dosing options. The convenience of taking a medication only monthly or weekly may improve adherence in patients who already have a large daily pill burden. Of the available oral bisphosphonates, the generic version of the weekly alendronate formulation is the least expensive. Parenteral bisphosphonates are administered even less frequently and can be better tolerated for patients who complain of gastrointestinal upset with the oral agents. Both parenteral options, ibandronate and zoledronic acid, cost approximately $300 per dose; however, zoledronic acid only requires one dose annually, whereas ibandronate is administered every 3 months, equating to an annual cost of $1200. Alternative options, such as calcitonin, teriparatide, and denosumab, are available as intranasal and subcutaneous formulations, respectively. Intranasal calcitonin is the least expensive, whereas teriparatide is the most costly, at an average wholesale price of over $2000 per month. Denosumab is relatively expensive as well, approximately $1000 per dose, but is only administered every 6 months [73]. In addition to cost, side effects and intensity of patient monitoring can also be barriers to adherence. Table 6 summarizes the side effects, contraindications, monitoring parameters, and recommended dosage adjustments for most of the agents discussed above. Taking all of these factors into consideration can also help to determine an optimal treatment regimen that aligns with patient preference in order to achieve excellent adherence.

Conclusion

Osteoporosis continues to place a heavy burden on solid organ transplant patients. Numerous risk factors both prior to and after transplantation, including immunosuppressive therapy, contribute to the increased likelihood that patients will

Table 6 Safety and monitoring of recommended treatment options

Medication	Dose adjustments	Side effects	Monitoring	Contraindications
Calcium [5] Calcium carbonate Calcium citrate	None	Constipation, flatulence, hypercalcemia, myocardial infarction, urolithiasis	Ca, Ph, PTH, 25(OH)D	Hypercalcemia
Vitamin D [5] Ergocalciferol Cholecalciferol	Adjust dose based on serum Ca concentration Discontinue if serum Ca >10.2 mg/dL or hyperphosphatemia persists despite phosphate binder treatment	Constipation, nausea, vomiting, hypercalcemia, hypervitaminosis D	Ca, Ph, and 25(OH)D	Hypervitaminosis D, hypercalcemia
Bisphosphonates [39–43, 47] Alendronate Ibandronate Pamidronate Risedronate Zoledronic acid	CrCl <30 mL/min (ibandronate, risedronate: not recommended) CrCl <35 mL/min (alendronate: not recommended) Scr >3 mg/dL or CrCl <30 mL/min: prolong infusion over 4–6 h and consider reducing initial dose (pamidronate)	Abdominal pain, constipation, diarrhea, nausea, indigestion, esophageal stricture, gastric ulcer; hypocalcemia, hypokalemia, hypomagnesemia; aseptic necrosis of the jaw, bone pain, osteonecrosis; nephrotoxicity	Scr, Ca, 25(OH)D	CrCl <35 mL/min (zoledronic acid); hypocalcemia Oral formulations: esophageal abnormalities, inability to stand or sit upright for 30 (alendronate, risedronate) to 60 (ibandronate) minutes after administration
Teriparatide [50]	None	Constipation, diarrhea, indigestion, nausea, vomiting; hypotension, syncope, angina; rash; hyperuricemia; arthralgia, spasm; dizziness; pharyngitis, rhinitis, cough Black box warning: dose and duration dependent increased incidence in osteosarcoma in rats. Do not prescribe in patients at increased risk for osteosarcoma REMS: 2 year maximum lifetime duration of treatment. Potential risk of osteosarcoma.	Ca; uric acid; urine Ca; signs and symptoms of osteosarcoma	None
Calcitonin [56]	None	Flushing, injection site reaction; nausea; arthralgia; epistaxis, rhinitis, sinusitis; hypocalcemia; seizure	Ca, Scr	
Denosumab [59]	None	Diarrhea, nausea, vomiting, pancreatitis; hypercholesterolemia, hypocalcemia, hypophosphatemia; anemia; arthralgia, backache, aseptic necrosis of bone; headache; cystitis; nasopharyngitis	Ca, Ph, Mg, 25(OH)D	Hypocalcemia; pregnancy

Ca calcium, *Ph* phosphorus, *Mg* magnesium, *PTH* parathyroid hormone, *Scr* serum creatinine

develop osteoporosis compared to the general population. Many treatment modalities have been investigated to combat the complex mechanisms leading to osteoporosis in this population. It is clear that all patients should maintain normal serum calcium and vitamin D levels which can be achieved through daily supplementation if required. Maintenance of normal calcium and phosphorus is imperative for parathyroid hormone homeostasis. At this point, treatment with bisphosphonates has the most robust evidence for increasing hip and spine BMD and preventing the loss in BMD that occurs immediately after transplantation. Patients' renal function must be evaluated upon initiation and throughout treatment, and the risk of adynamic bone disease should be weighed against the potential benefits of using bisphosphonates especially in those recovering from years of end-stage CKD. Evidence for the use of subcutaneous teriparatide in the transplant population is yet to be shown, and while treatment may not result in significant adverse effects with short-term use, it is unlikely any true benefit will result in this population. Intranasal calcitonin is also a possible adjunctive therapy with calcium and vitamin D in those who cannot tolerate bisphosphonate therapy. On the other hand, denosumab should theoretically result in improved BMD in this population based on its mechanism of action, and is currently being investigated for use in kidney transplant patients. Hormone replacement therapy may be an option for postmenopausal women or patients with hypogonadism; however, the evidence for its efficacy in this population is limited. Immunosuppressant regimens that reduce the intensity of steroid treatment have been associated with a number of potential benefits, some of which may be improvements in BMD and rates of fractures, and should be utilized whenever appropriate. Alternatively, adding sirolimus to maintenance regimens may help to improve BMD as well, although studies directly evaluating benefits on BMD and rates of fractures need to be conducted. Overall, most studies in this population are limited by small sample sizes, so additional evidence for novel therapies is required before the full benefit of these treatments can be assessed. The optimal dosing and duration of bisphosphonate therapy, as well as the true impact on fracture rates in transplant patients, still remain unanswered. Working with a pharmacist to evaluate the risks and benefits of each treatment option in an effort to determine the most appropriate therapy would be beneficial when treating this complex patient population.

Compliance with ethical standards

Conflict of interest Caitlin Rose Early, Linda Stuckey, and Sarah Tischer declare they have no conflict of interest.

References

1. Sayegh MH, Carpenter CB (2004) Transplantation 50 years later—progress, challenges, and promises. N Engl J Med 351:2761–2766
2. Yu TM, Lin CL, Chang SN, Sung FC, Huang ST, Kao CH (2014) Osteoporosis and fractures after solid organ transplantation: a nationwide population-based cohort study. Mayo Clin Proc 89:888–895
3. Kulak CA, Borba VZ, Kulak J Jr, Custodio MR (2012) Osteoporosis after transplantation. Curr Osteoporos Rep 10:48–55
4. Maalouf NM, Shane E (2005) Osteoporosis after solid organ transplantation. J Clin Endocrinol Metab 90:2456–2465
5. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R (2014) Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 25:2359–2381
6. Wibaux C, Legroux-Gerot I, Dharancy S, Boleslawski E, Declerck N, Canva V, Mathurin P, Pruvot FR, Cortet B (2011) Assessing bone status in patients awaiting liver transplantation. Joint Bone Spine 78:387–391
7. Gal-Moscovici A, Sprague SM (2007) Osteoporosis and chronic kidney disease. Semin Dial 20:423–430
8. Wang TK, O'Sullivan S, Gamble GD, Ruygrok PN (2013) Bone density in heart or lung transplant recipients—a longitudinal study. Transplant Proc 45:2357–2365
9. Grossman JM, Gordon R, Ranganath VK et al (2010) American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res 62:1515–1526
10. Costanzo MR, Dipchand A, Starling R et al (2010) The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant Off Publ Int Soc Heart Transplant 29:914–956
11. Lucey MR, Terrault N, Ojo L, Hay JE, Neuberger J, Blumberg E, Teperman LW (2013) Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc 19:3–26
12. Kidney Disease: Improving Global Outcomes Transplant Work G (2009) KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surgeons 9(Suppl 3):S1–155
13. Bia M, Adey DB, Bloom RD, Chan L, Kulkarni S, Tomlanovich S (2010) KDOQI US commentary on the 2009 KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Kidney Dis Off J Natl Kidney Found 56:189–218
14. Schipper LG, Fleuren HW, van den Bergh JP, Meinardi JR, Veldman BA, Kramers C (2015) Treatment of osteoporosis in renal insufficiency. Clin Rheumatol (2015) 34:1341–1345. doi:10.1007/s10067-015-2883-4
15. Jamal SA, West SL, Miller PD (2012) Bone and kidney disease: diagnostic and therapeutic implications. Curr Rheumatol Rep 14:217–223
16. Mitterbauer C, Oberbauer R (2008) Bone disease after kidney transplantation. Transplant Int Off J Eur Soc Organ Transplant 21:615–624
17. Stein EM, Shane E (2011) Vitamin D in organ transplantation. Osteoporos Int A J Estab Result Coop Eur Found Osteoporos Natl Osteoporos Found USA 22:2107–2118
18. Bitetto D, Fabris C, Falleti E et al (2010) Vitamin D and the risk of acute allograft rejection following human liver transplantation. Liver Int Off J Int Assoc Study Liver 30:417–444
19. Obi Y, Hamano T, Ichimaru N et al (2014) Vitamin D deficiency predicts decline in kidney allograft function: a prospective cohort study. J Clinical Endocrinol Metabol 99:527–535

20. Lowery EM, Bemiss B, Cascino T, Durazo-Arvizu RA, Forsythe SM, Alex C, Laghi F, Love RB, Camacho P (2012) Low vitamin D levels are associated with increased rejection and infections after lung transplantation. J Heart Lung Transplant Off Publ Int Soc Heart Transplant 31:700–707
21. Grotz W, Nagel C, Poeschel D et al (2001) Effect of ibandronate on bone loss and renal function after kidney transplantation. J Am Soc Nephrol 12:1530–1537
22. Coco M, Glicklich D, Faugere MC et al (2003) Prevention of bone loss in renal transplant recipients: a prospective, randomized trial of intravenous pamidronate. J Am SocNephrol 14:2669–2676
23. Schwarz C, Mitterbauer C, Heinze G, Woloszczuk W, Haas M, Oberbauer R (2004) Nonsustained effect of short-term bisphosphonate therapy on bone turnover three years after renal transplantation. Kidney Int 65:304–309
24. Fahrleitner-Pammer A, Piswanger-Soelkner JC, Pieber TR et al (2009) Ibandronate prevents bone loss and reduces vertebral fracture risk in male cardiac transplant patients: a randomized double-blind, placebo-controlled trial. J Bone Miner Res Off J Am Soc Bone Miner Res 24:1335–1344
25. Shane E, Cohen A, Stein EM et al (2012) Zoledronic acid versus alendronate for the prevention of bone loss after heart or liver transplantation. J Clin Endocrinol Metabol 97:4481–4490
26. Nowacka-Cieciura E, Cieciura T, Baczkowska T, Kozinska-Przybyl O, Tronina O, Chudzinski W, Pacholczyk M, Durlik M (2006) Bisphosphonates are effective prophylactic of early bone loss after renal transplantation. Transplant Proc 38:165–167
27. Torregrosa JV, Fuster D, Pedroso S, Diekmann F, Campistol JM, Rubí S, Oppenheimer F (2007) Weekly risedronate in kidney transplant patients with osteopenia. Transpl Int 20:708–711
28. Omidvar B, Ghorbani A, Shahbazian H, Beladi Mousavi SS, Shariat Nabavi SJ, Alasti M (2011) Comparison of alendronate and pamidronate on bone loss in kidney transplant patients for the first 6 months of transplantation. Iran J Kidney Dis 5:420–424
29. Torregrosa JV, Fuster D, Monegal A, Gentil MA, Bravo J, Guirado L, Muxi A, Cubero J (2011) Efficacy of low doses of pamidronate in osteopenic patients administered in the early post-renal transplant. Osteoporos Int J Estab Result Coop Eur Found Osteoporos Natl Osteoporos Found USA 22:281–287
30. Gilfraguas L, Guadalix S, Martinez G, Jodar E, Vara J, Gomez-Sanchez MA, Delgado J, De La Cruz J, Lora D, Hawkins F (2012) Bone loss after heart transplant: effect of alendronate, etidronate, calcitonin, and calcium plus vitamin D3. Prog Transplant (Aliso Viejo, Calif) 22:237–243
31. Millonig G, Graziadei IW, Eichler D, Pfeiffer KP, Finkenstedt G, Muehllechner P, Koenigsrainer A, Margreiter R, Vogel W (2005) Alendronate in combination with calcium and vitamin D prevents bone loss after orthotopic liver transplantation: a prospective single-center study. Liver Transplant Off Publ Am Assoc Study Liver DisInt Liver Transplant Soc 11:960–966
32. Atamaz F, Hepguler S, Akyildiz M, Karasu Z, Kilic M (2006) Effects of alendronate on bone mineral density and bone metabolic markers in patients with liver transplantation. Osteoporos Int J Estab Result Coop Eur Found Osteoporos Natl Osteoporos Found USA 17:942–949
33. Crawford BA, Kam C, Pavlovic J, Byth K, Handelsman DJ, Angus PW, McCaughan GW (2006) Zoledronic acid prevents bone loss after liver transplantation: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 144:239–248
34. Bodingbauer M, Wekerle T, Pakrah B et al (2007) Prophylactic bisphosphonate treatment prevents bone fractures after liver transplantation. Am J Transplant Off J Am Soc Transplant Am SocTransplant Surg 7:1763–1769
35. Monegal A, Guanabens N, Suarez MJ et al (2009) Pamidronate in the prevention of bone loss after liver transplantation: a randomized controlled trial. Transplant Int Off J Eur Soc Organ Transplant 22:198–206
36. Guadalix S, Martínez-Díaz-Guerra G, Lora D, Vargas C, Gómez-Juaristi M, Cobaleda B, González EM, Hawkins F (2011) Effect of early risedronate treatment on bone mineral density and bone turnover markers after liver transplantation: a prospective single-center study. Transpl Int 24:657–665
37. Kaemmerer D, Schmidt B, Lehmann G, Wolf G, Hommann M, Settmacher U (2012) Monthly ibandronate for the prevention of bone loss in patients after liver transplantation. Transplant Proc 44:1362–1367
38. Palmer SC, McGregor DO, Strippoli GF (2007) Interventions for preventing bone disease in kidney transplant recipients. Cochrane Database Syst Rev CD005015
39. Alendronate [package insert]. Whitehouse Station, NJ: Merck & Co., Inc. 2012
40. Ibandronate sodium injection [package insert] San Francisco, CA: Genentech, Inc. 2013
41. Ibandronate sodium tablets [package insert] Research Triangle Park, NC: GlaxoSmithKline 2005
42. Risedronate [package insert] Mason, OH: Warner Chilcott Pharmaceuticals Inc. 2010
43. Zoledronic Acid [package insert] East Hanover, NJ: Novartis 2015
44. Jamal SA, Bauer DC, Ensrud KE, Cauley JA, Hochberg M, Ishani A, Cummings SR (2007) Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. J Bone Miner Res Off J Am Soc Bone Miner Res 22:503–508
45. Hirschberg R (2012) Renal complications from bisphosphonate treatment. Curr Opin Supp Palliat Care 6:342–347
46. Berenson JR, Boccia R, Lopez T, Warsi GM, Argonza-Aviles E, Lake S, Ericson SG, Collins R (2011) Results of a multicenter open-label randomized trial evaluating infusion duration of zoledronic acid in multiple myeloma patients (the ZMAX trial). J Support Oncol 9:32–40
47. Pamidronate [package insert] East Hanover, NJ: Novartis 2012
48. Black DM, Schwartz AV, Ensrud KE et al (2006) Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA 296:2927–2938
49. Watts NB, Bilezikian JP, Camacho PM et al (2010) American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of postmenopausal osteoporosis. Endoc Pract Off J Am College Endocrinol Am Assoc Clin Endocrinol 16(Suppl 3):1–37
50. Teriparatide [package insert] Indianapolis, IN: Eli Lilly and Company 2012
51. Saag KG, Zanchetta JR, Devogelaer JP, Adler RA, Eastell R, See K, Krege JH, Krohn K, Warner MR (2009) Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. Arthritis Rheum 60:3346–3355
52. Cejka D, Benesch T, Krestan C, Roschger P, Klaushofer K, Pietschmann P, Haas M (2008) Effect of teriparatide on early bone loss after kidney transplantation. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg 8:1864–1870
53. Wang HH, Chang PC, Chu SH, Liu KL, Lai PC, Huang JY, Chiang YJ (2008) Osteoporosis after kidney transplantation: preliminary report from a single center. Transplant Proc 40:2412–2413
54. Kapetanakis EI, Antonopoulos AS, Antoniou TA, Theodoraki KA, Zarkalis DA, Sfirakis PD, Chilidou DA, Alivizatos PA (2005) Effect of long-term calcitonin administration on steroid-induced osteoporosis after cardiac transplantation. J heart Lung transplant Off Publ Int Soc Heart Transplant 24:526–532
55. Bianda T, Linka A, Junga G, Brunner H, Steinert H, Kiowski W, Schmid C (2000) Prevention of osteoporosis in heart transplant

recipients: a comparison of calcitriol with calcitonin and pamidronate. Calcif Tissue Int 67:116–121
56. Calcitonin-salmon [package insert] East Hanover, NJ: Novartis 2014
57. Cummings SR, San Martin J, McClung MR et al (2009) Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 361:756–765
58. Leder BZ, Tsai JN, Uihlein AV, Burnett-Bowie SA, Zhu Y, Foley K, Lee H, Neer RM (2014) Two years of Denosumab and teriparatide administration in postmenopausal women with osteoporosis (The DATA Extension Study): a randomized controlled trial. J Clin Endocrinol Metab 99:1694–1700
59. Denosumab [package insert] Thousand Oaks, CA: Amgen Inc. 2015
60. Cohen SB, Dore RK, Lane NE et al (2008) Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. Arthritis Rheum 58:1299–1309
61. Bonani M, Serra AL, Fehr T, Brockmann J, Schiesser M, Frey DP, Wüthrich RP (2012) A randomized open label clinical trial examining the effect of denosumab on the prevention of first year bone mineral density loss after renal transplantation (POSTOP Study; NCT01377467): 1515. Transplantation 94(10S):887
62. Vasikaran S, Eastell R, Bruyere O et al (2011) Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporos Int J Estab Result Coop Eur Found Osteoporos Natl Osteoporos Found USA 22:391–420
63. Ettinger B, Black DM, Mitlak BH et al (1999) Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 282:637–645
64. Hernandez E, Valera R, Alonzo E, Bajares-Lilue M, Carlini R, Capriles F, Martinis R, Bellorin-Font E, Weisinger JR (2003) Effects of raloxifene on bone metabolism and serum lipids in postmenopausal women on chronic hemodialysis. Kidney Int 63:2269–2274
65. Isoniemi H, Appelberg J, Nilsson CG, Makela P, Risteli J, Hockerstedt K (2001) Transdermal oestrogen therapy protects postmenopausal liver transplant women from osteoporosis. A 2-year follow-up study. J Hepatol 34:299–305
66. Stempfle HU, Werner C, Echtler S, Wehr U, Rambeck WA, Siebert U, Uberfuhr P, Angermann CE, Theisen K, Gartner R (1999) Prevention of osteoporosis after cardiac transplantation: a prospective, longitudinal, randomized, double-blind trial with calcitriol. Transplantation 68:523–530
67. Fleischer J, McMahon DJ, Hembree W, Addesso V, Longcope C, Shane E (2008) Serum testosterone levels after cardiac transplantation. Transplantation 85:834–839
68. Pereira S, Pedroso S, Martins L et al (2010) Bone mineral density after simultaneous kidney-pancreas transplantation: four years follow-up of 57 recipients. Transplant Proc 42:555–557
69. Vincenti F, Schena FP, Paraskevas S, Hauser IA, Walker RG, Grinyo J, Group FS (2008) A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg 8:307–316
70. Woodle ES, First MR, Pirsch J, Shihab F, Gaber AO, Van Veldhuisen P, Astellas Corticosteroid Withdrawal Study G (2008) A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. Ann Surg 248:564–577
71. Edwards BJ, Desai A, Tsai J, Du H, Edwards GR, Bunta AD, Hahr A, Abecassis M, Sprague S (2011) Elevated incidence of fractures in solid-organ transplant recipients on glucocorticoid-sparing immunosuppressive regimens. J Osteoporos 2011:591793
72. Westenfeld R, Schlieper G, Woltje M, Gawlik A, Brandenburg V, Rutkowski P, Floege J, Jahnen-Dechent W, Ketteler M (2011) Impact of sirolimus, tacrolimus and mycophenolate mofetil on osteoclastogenesis–implications for post-transplantation bone disease. Nephrol Dial Transplant Off Publ Eur Dial Transplant Assoc Eur Renal Assoc 26:4115–4123
73. Red Book Online [database online]. Greenwood Village, CO: Truven Health Analytics, Inc. Updated periodically. Accessed 3 March 2015