Osteoporosis in Organ Transplant Patients

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11.1 Skeletal Effects of Immunosuppressive Drugs

11.1.1 The Bone-Remodeling System

Bone remodeling is an orderly series of events in which old, damaged bone is replaced by new, mechanically stronger bone. Osteoclast first excavates small (0.5 mm^3) resorption pits or Howship's lacunae on cancellous and cortical bone surfaces, a process that takes 2–3 weeks (Ross 2006). After a brief rest period (the reversal phase), local mesenchymal marrow stem cells differentiate into osteoblasts and accumulate in the resorption pits (Aubin et al. 2006). Clusters of plump cuboidal osteoblasts first produce new bone matrix or osteoid and then mineralize it. Osteoclasts express receptors for NFkB ligand (RANKL), calcitonin, prostaglandins, calcium, and vitronectin (integrin $\alpha_1\beta_3$). Osteoblasts express receptors for several hormones (parathyroid hormone, estrogens, vitamin D_3), cell adhesion molecules (integrins), and cytokines. Bone remodeling is regulated by the tumor necrosis factor (TNF) ligand and receptor-signaling family: RANKL, RANK, and osteoprotegerin (OPG) (Gori et al. 2000; Hofbauer et al. 2000). RANKL is expressed by osteoblasts and by bone marrow stromal cells. In the presence of sufficient macrophage colony-stimulating factor (mCSF), RANKL binds to RANK receptors on surfaces of osteoclast lineage cells, resulting in rapid differentiation of osteoclast precursors to mature osteoclasts, increased osteoclast activity, and reduced apoptosis of mature

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osteoclasts. RANKL also binds to another osteoblast product, OPG. Competitive binding of RANKL to either RANK or OPG regulates bone remodeling by increasing (RANK) or decreasing (OPG) osteoclastogenesis. Immunosuppressants exert their effects on remodeling by interacting with the RANK/RANKL/OPG system (Hofbauer et al. 2001). When bone remodeling becomes "uncoupled," such that the rate of resorption exceeds the rate of formation, bone loss occurs. Transplantation-related bone loss results from both an increase in the rate of bone resorption and a decrease in the rate of bone formation (Cohen et al. 2006a; Epstein 1996).

11.1.2 Glucocorticoids

Glucocorticoids (GCs), which are well recognized to cause osteoporosis, are included in the majority of posttransplant immunosuppression regimens. Prednisone or methylprednisolone is often prescribed in high doses (50–100 mg of prednisone or its equivalent daily) immediately after transplantation and during episodes of severe rejection, with gradual reduction over weeks to months. Total exposure varies with the organ transplanted, the number and management of rejection episodes, and the practice of individual transplantation programs.

The mechanisms by which GCs cause bone loss and fractures have been summarized in several reviews (Mazziotti et al. 2006; Sambrook 2006; van Staa 2006; Kulak et al. 2012; Amiche et al. 2016). Their predominant effect is an immediate and profound inhibition of bone formation: decreased osteoblast recruitment, differentiation and synthesis of type I collagen, induction of osteoblast and osteocyte apoptosis, and stimulation of osteocyte autophagy (Weinstein et al. 1998; Piemontese et al. 2015). Mechanistically, increased microRNA expression in osteoblasts exposed to GCs suppresses Wnt signaling, which is important for osteoblast expansion and function (Shi et al. 2015a; Westendorf et al. 2004). These effects are reflected biochemically by low serum levels of osteocalcin, a major non-collagenous bone matrix protein secreted by osteoblasts. GCs also inhibit growth hormone secretion and decrease production or bioactivity of certain skeletal growth factors (IGF-1, PGE$_2$, and TGF-β), actions that also reduce bone formation.

GCs also increase bone resorption by decreasing osteoblast expression of OPG and increasing osteoblast expression of RANKL. The effects of GCs on osteoclast formation and function are dose dependent and mediated via increases in reactive oxygen species, which facilitate osteoclastogenesis (Shi et al. 2015b). GC stimulatory effects on resorption are not as profound as their inhibitory effects on formation and are generally limited to the first 6–12 months. GCs may be associated with secondary hyperparathyroidism due to inhibition of intestinal calcium absorption and stimulation of urinary calcium excretion. Multiple studies have shown direct relationships between serum PTH levels and rates of bone loss after organ transplantation (Gupta et al. 2012; Torregrosa et al. 1995; Savaj and Ghods 2012; Obi et al. 2014; Mazzaferro and Pasquali 2016). GCs also cause hypogonadotrophic hypogonadism and reduced secretion of adrenal androgens and estrogens, which may also increase bone resorption. These contrasting effects of GCs upon bone formation (decreased) and

resorption (increased) prevent osteoblasts from replacing the increased amount of bone resorbed at each remodeling site, and rapid bone loss ensues.

New data suggest that GCs decrease bone strength as well as bone mass (Mellibovsky et al. 2015). Reference point indentation of the anterior tibia allows tissue-level assessment of bone mechanical characteristics and detects subtle treatment-induced changes in bone material properties (Mellibovsky et al. 2015). In 52 patients tested within 4 weeks of GC initiation, strength declined in those on GCs for 7 and 20 weeks (Mellibovsky et al. 2015). In contrast, bone densitometry (BMD) by DXA did not decline, suggesting that subtle changes in bone material strength occur soon after GC initiation, before bone loss is detected by DXA (Mellibovsky et al. 2015).

GCs cause bone loss in individuals of all races, ages, and of both genders. However, postmenopausal Caucasian women, in whom GC effects are superimposed upon bone loss due to aging and estrogen deficiency, are at greatest risk for fracture (Sambrook 2006; van Staa 2006). In general, bone loss is most rapid during the first 12 months and is directly related to dose and duration of therapy. Areas of the skeleton rich in cancellous bone (ribs, vertebrae, and distal ends of long bones) and the cortical rim of the vertebral body are most severely affected and are the most common sites for fracture. This bone loss can be tempered with the use of anti-osteoporosis medications (Overman et al. 2015). One study found a 48 % decrease in fractures by 1 year and a 32 % decrease by 3 years if patients on GCs are treated with agents such as bisphosphonates, denosumab, or teriparatide within 90 days of GC initiation (Overman et al. 2015).

11.1.3 Calcineurin Inhibitors

Cyclosporine A (*CsA*) was introduced to posttransplant immunosuppression regimens in the early 1980s. CsA is a small fungal cyclic peptide that forms a heterodimer with its cytoplasmic receptor, cyclophilin, and inhibits phosphatase activity of calcineurin, which also regulates osteoblasts and osteoclasts (Kahan 1989; Sun et al. 2005; Sun et al. 2007). The calcineurin gene has been identified in osteoclasts and extracted whole rat bone, but does not appear to be affected by CsA administration (Awumey et al. 1999). When administered to rodents, albeit in doses higher than those currently used to prevent allograft rejection, CsA was associated with a marked increase in osteoclast-mediated bone resorption and rapid and severe cancellous bone loss (Epstein 1996; Tamler and Epstein 2006; Movsowitz et al. 1988, 1989), likely mediated by T lymphocytes (Buchinsky et al. 1996; Rucinski et al. 1994; Zahner et al. 1997). CsA also increases gene expression of the bone-resorbing cytokines, IL-1 and IL-6(Marshall et al. 1995). In contrast to GCs, bone formation is increased in CsA-treated animals, although insufficiently to compensate for the increased resorption. Rodent studies suggest that hepatic clearance of CsA was six times lower in male than female rats, leading to increased rates of osteopenia (Jager et al. 2012), although this has not been shown in humans. CsA-induced bone loss may be promoted by PTH (Epstein et al. 2001). Drugs that inhibit bone resorption (estrogen, raloxifene, calcitonin, alendronate) prevent or attenuate CsA-induced bone loss in the rat (Bowman

et al. 1995; Joffe et al. 1992; Sass et al. 1997; Stein et al. 1991). Similarly, 1,25(OH)$_2$D and prostaglandin E2 prevent bone loss in CsA-treated rats (Epstein et al. 1990; Katz et al. 1992). Regimens that combine CsA with GCs found an additive rather than synergistic effect on bone loss (Shimizu et al. 2013).

Human studies have yielded conflicting results. Although kidney transplant patients receiving CsA in a GC-free regimen did not lose bone (Ponticelli and Aroldi 2001; Grotz et al. 1994; McIntyre et al. 1995; Cueto-Manzano et al. 2003), a prospective study found that cumulative CsA dose was associated with bone loss in the 2 years following transplant, independent of GCs (Josephson et al. 2004). In a recent study of patients on GC-sparing regimens, 27 % sustained a fracture within 6 months after transplant, similar to rates in patients on conventional GC-containing regimens (Edwards et al. 2011).

Tacrolimus (*FK506*), a macrolide that binds to an immunophilin FK-binding protein, blocks T-cell activation in a similar manner to CsA. FK506 causes bone loss in rodents similar in degree and mechanism to that observed with CsA (Cvetkovic et al. 1994). Rapid bone loss has been documented in patients after both cardiac (Stempfle et al. 1998) and liver (Park et al. 1996) transplantation. Rates of bone loss are directly associated with serum levels of FK506 (Luo et al. 2012). High serum FK506 levels were associated with high serum tartrate-resistant acid phosphatase (TRAP-5b) levels in male kidney transplant recipients, suggesting accelerated bone resorption as the underlying mechanism for FK506-mediated bone loss (Luo et al. 2012). FK506 may cause less bone loss than CsA (Goffin et al. 2002; Monegal et al. 2001a), likely because lower doses of GCs are required for immunosuppression. Whether FK506 confers any benefit over CsA with regard to fracture incidence is not known.

11.1.4 Other Immunosuppressive Agents

Sirolimus (rapamycin), a macrocyclic lactone, is structurally similar to FK506 and binds to the same binding protein, but induces immunosuppression via distinct mechanisms. In rat studies, low-dose CsA combined with rapamycin was bone sparing (Goodman et al. 2001). In an open-label study, markers of bone turnover (N-telopeptide and osteocalcin) were lower in kidney transplant recipients who received sirolimus than CsA; as BMD was not measured, no data on bone loss are available (Campistol et al. 2005). Mycophenolate mofetil does not have deleterious effects on bone in the rat (Dissanayake et al. 1998). The skeletal effects of other immunosuppressant agents such as mizoribine, deoxyspergualin, brequinar sodium, leflunomide, and azaspirane are unclear.

11.2 Vitamin D, Immunity, and Graft Rejection

Effects of vitamin D on immune function may be relevant after organ transplantation (Mazzaferro and Pasquali 2016; Lemire 1995; Stein and Shane 2011). Vitamin D potentiates the innate immune system and may protect against bacterial infections

and tuberculosis (Bikle 2008). When $1,25(OH)_2D$ is produced by monocytes and macrophages in sufficient quantities, it has intracellular antimicrobial effects. $1,25(OH)_2D$ can also interact with and govern the cytokine profiles of activated T and B lymphocytes (Adams and Hewison 2010a). The ability of monocytes and macrophages to synthesize $1,25(OH)_2D$ is dependent on the availability of adequate serum concentrations of 25-OHD and increases in response to vitamin D supplementation (Adams and Hewison 2010a). When sufficient 25-OHD is not available, there are declines in both local production of $1,25(OH)_2D$ and activity of $1,25(OH)_2D$ against ingested microbes (Adams and Hewison 2010b). The antimicrobial actions of $1,25(OH)_2D$ also occur in barrier epithelial cells of the skin (Peric et al. 2008; Schauber et al. 2008), gut (Liu et al. 2008), and lungs (Hansdottir et al. 2008). Animals treated with the $1,25(OH)_2D$ analogue, calcitriol, were resistant to infection with *Candida albicans* and *Herpes simplex virus*-1 (Cantorna et al. 1998), two common opportunistic infections in transplant patients.

There is evidence supporting a role for vitamin D in the regulation of immune cell proliferation, differentiation, and responsiveness (Lemire 1995; Bikle 2011; Haroon and Fitzgerald 2012; Dimitrov et al. 2014; Adams et al. 2014; Wei and Christakos 2015). Animal studies suggest that $1,25(OH)_2D$ prevents acute allograft rejection following liver (Zhang et al. 2003; Redaelli et al. 2001), kidney (Becker et al. 2002), and heart (Hullett et al. 1998) transplantation. While there are limited data from human studies, kidney transplant recipients supplemented with calcitriol had fewer episodes of acute cellular rejection (Tanaci et al. 2003), required lower GC doses (Uyar et al. 2006), and had decreased expression of co-stimulatory and HLA-DR molecules (Ahmadpoor et al. 2009). In one study, patients treated with calcitriol after heart transplantation required less CsA (Briffa et al. 2003). In contrast, our study of heart transplant recipients found no differences between those randomized to calcitriol and alendronate with respect to CsA or prednisone dose (Shane et al. 2004). In a retrospective study of cardiac transplant patients, those with lower preoperative serum 25-OHD levels had more moderate-to-severe rejection episodes in the first 2 months after transplant (Bitetto et al. 2010). In 293 kidney transplant recipients, low serum 25-OHD levels predicted both decline in GFR and requirement for GCs to treat allograft rejection (Obi et al. 2014). In an observational study of liver transplant patients, those supplemented with cholecalciferol had fewer rejection episodes (Bitetto et al. 2010). Several studies have found increased BMD at the lumbar spine and femoral neck in renal transplant patients receiving activated vitamin D (calcitriol and alfacalcidol) (Sarno et al. 2015; Courbebaisse et al. 2014). The optimal amount of cholecalciferol that is both beneficial and safe in transplant recipients remains to be determined. The vitamin D supplementation in renAL transplant recipients (VITALE) trial is a prospective, multicenter, randomized trial of the efficacy and safety of cholecalciferol 100,000 IU monthly to maintain serum levels of 25-hydroxyvitamin D between 30 and 80 ng/mL (Courbebaisse et al. 2014). The results of this study will be interesting especially in light of studies that have found higher rates of falls and fractures in people treated with high doses of cholecalciferol (Sanders et al. 2010; Bischoff-Ferrari et al. 2016).

11.3 Effect of Transplantation on Bone and Mineral Metabolism

11.3.1 Bone Loss Before Transplantation

Many patients awaiting organ transplantation have multiple established risk factors for osteoporosis (older age, hypogonadism, physical inactivity, excessive tobacco and alcohol use, and exposure to drugs known to cause bone loss, such as GCs, heparin, loop diuretics). Most have already sustained considerable bone loss (Shane et al. 1997a; Ball et al. 2002; Hay 2003).

11.3.2 Kidney and Kidney-Pancreas Transplantation

Chronic kidney disease-mineral and bone disorder (CKD-MBD) refers to complex abnormalities in bone and mineral metabolism that affect most patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD). Factors that contribute to development of CKD-MBD include disturbances in calcium and phosphate metabolism, low serum 25-OHD levels and decreased calcitriol synthesis, increased synthesis and secretion of PTH, metabolic acidosis, and defective bone mineralization (Martin et al. 2006; Beique et al. 2013). Patients with CKD-MBD may manifest extraskeletal calcifications, abnormal immune and cardiovascular function, and variable abnormalities in bone histology termed renal osteodystrophy (ROD). Almost 70–90 % of CKD stage 2–4 patients and all with stage 5 CKD have some form of ROD: high bone turnover with or without osteitis fibrosa (due to hyperparathyroidism), low bone turnover or adynamic bone disease, osteomalacia, or "mixed" renal osteodystrophy, a combination of one or more of the aforementioned lesions. The specific histological type depends on many factors that regulate bone remodeling and mineralization, such as PTH, acidosis, hypogonadism, and type I diabetes, as well as various therapeutic interventions used to manage patients with CKD and ESRD. Measurement of BMD by Dual-energy X-ray absorptiometry (DXA) does not distinguish among the various types of ROD. Fracture risk is estimated to be 4.4–14 times greater in patients with ESRD than the general population (Coco and Rush 2000; Mittalhenkle et al. 2004). In one study, 34 % of hemodialysis (HD) patients had a history of previous fracture (Kohlmeier et al. 1998). In another, fracture incidence was 0.1 per dialysis year in patients with osteitis fibrosa and 0.2 per dialysis year in patients with adynamic bone disease (Piraino et al. 1988). In people with moderate-to-severe CKD not on HD, hip fractures are twice as common as in those with normal kidney function (Nickolas et al. 2006).

As patients with ESRD are highly likely to have compromised bone health before kidney transplantation, it is not surprising that low spine and/or hip BMD has been reported in many cross-sectional studies of long-term kidney transplant recipients (Gupta et al. 2012; Grotz et al. 1994; Shane 2003; Cohen and Shane 2003; Epstein and Shane 2001; Shane and Epstein 2001; Braga Junior et al. 2006; Dolgos et al. 2008; Marcen et al. 2007; Dounousi et al. 2015; Boot et al. 1995; Cueto-Manzano

et al. 1999), although the prognostic significance of low BMD in this group is unclear. Depending on the study and site of measurement, prevalence of low BMD long-term kidney transplant recipients ranges between 11 and 41 %. Factors associated with low BMD include increasing time since transplantation, high PTH concentrations, advanced age, female gender, and diabetic nephropathy.

A large number of longitudinal studies have documented high rates of bone loss at the spine and hip after kidney transplantation, ranging from 3 to 10 % during the first 6–12 months (Torregrosa et al. 1995; Savaj and Ghods 2012; Almond et al. 1994; Gallego et al. 2006; Horber et al. 1994; Kwan et al. 1992; Mikuls et al. 2003; Techawathanawanna et al. 2005; Yun et al. 1996; Bayat et al. 2007). Several studies have reported that GC dose is directly associated with bone loss (Rizzari et al. 2012; Woodle et al. 2008). However, by early 2000s, most kidney transplant programs were using lower GC doses and an increasing number of programs discontinue GCs altogether a few days after surgery. This shift in management seems to be associated with both reduced rates of bone loss and recovery of bone loss to pretransplant levels by 2 years after kidney transplantation in some (Aroldi et al. 1997; van den Ham et al. 2003; Nishioka et al. 2014), although not all studies (Meulen et al. 2004). For example, in 326 patients who had received a kidney transplant between 1996 and 2011, BMD Z scores were only slightly below average for age and sex at the baseline exam (approximately 6 months after transplant) and were not different from normal at 2.7 years (Naylor et al. 2014). In 47 patients managed without GCs and followed for 1 year after kidney transplant, DXA did not detect any bone loss at the spine or hip (Iyer et al. 2014). On a cautionary note, however, DXA did detect significant bone loss at the ultradistal and 1/3 radius sites, which are seldom measured (Iyer et al. 2014). Thus, despite the lower doses of GCs and alternative antirejection drugs used today (Gaston 2006; Paterson et al. 2005; Pescovitz 2006; Regazzi et al. 2005), significant bone loss occurs, although it may be less rapid than documented in the 1980s and 1990s (Van Staa et al. 2000). Moreover, high-resolution peripheral quantitative computed tomography (HRpQCT), which separately measures cortical and trabecular volumetric BMD and microarchitecture at the distal radius and tibia, documented cortical and trabecular bone loss and significant decreases in whole bone strength (Iyer et al. 2014). Cortical bone loss was directly related to an increase in cortical porosity at the endocortical surface and to higher PTH levels (Nishiyama et al. 2015). In contrast, seven patients, in whom GCs were stopped shortly after kidney transplantation and who underwent transiliac bone biopsy within 2 months and again 2–5 years after surgery, showed significant deterioration of trabecular bone microstructure, no significant changes in cortical bone, and no relationship between cortical bone parameters and PTH (Carvalho et al. 2015).

Fractures after renal transplantation typically affect appendicular sites (feet, ankles, long bones, hips) more than axial sites (spine, ribs) (Roe et al. 2005). In one study, non-vertebral fractures were far more prevalent in renal transplant recipients than in the normal population (Ramsey-Goldman et al. 1999), although another study found that renal transplant recipients had a lower risk of non-vertebral fracture compared to members of the general population who had previously sustained

a non-vertebral fracture (Naylor et al. 2015). More recent data from a large cohort of first-time kidney transplant recipients suggests that hip fracture incidence may be lower in recent years with a hazard ratio for new hip fracture in the year 2010 of 0.56 (0.41–0.77) when compared to 1997 (Sukumaran Nair et al. 2014); this is noteworthy as patients transplanted in 2010 were older and had more medical comorbidities than the 1997 cohort (Sukumaran Nair et al. 2014). In a 3-year retrospective study of 35 kidney-pancreas recipients, approximately half had sustained from one to three symptomatic, non-vertebral fractures (Chiu et al. 1998). Men with type 1 diabetes who undergo kidney-pancreas transplants were recently reported to have approximately 30 % lower fracture rates than those who undergo kidney transplant alone; this relationship was not seen among women (Nikkel et al. 2011, 2013). Older age, white race, prior dialysis, and pretransplantation fracture were associated with increased fracture risk (Nikkel et al. 2013). Fracture incidence may be lower in patients managed with early GC withdrawal (Nikkel et al. 2012). A recent systematic review of fracture incidence in kidney transplant recipients analyzed 10 studies totaling 262,678 recipients and found a highly variable incidence rate ranging from 3.3 to 99.6 fractures per 1000 person-years (Naylor et al. 2013). Similarly, the 5-year cumulative incidence for fracture varied ranging from 0.85 to 27 %. Common factors associated with increased fracture risk were older age, female sex, the presence of diabetes, and receipt of dialysis before transplantation (Naylor et al. 2013). Other less common but statistically significant risk factors were a previous history of fracture and receipt of a kidney from a deceased versus living donor (Naylor et al. 2013). The authors concluded that there is poor consensus on the incidence and risk factors for fractures in kidney transplant recipients.

After kidney transplantation, there are several fairly consistent changes in biochemical indices of mineral metabolism and bone turnover (Julian et al. 1991; Kulak and Shane 2006; Sprague et al. 2008; Molnar et al. 2014; Alshayeb et al. 2013). PTH levels are often very high before transplantation, and while levels typically decline markedly immediately after transplantation (Akaberi et al. 2006; Rathi et al. 2015), they may remain above normal throughout the first year (Iyer et al. 2014) and may never completely normalize. Mild hypercalcemia and hypophosphatemia are common during the first few months after transplant (Rathi et al. 2015), but usually resolve within a few months. In long-term transplant recipients, persistent elevations in PTH may be associated with reduced hip BMD (Akaberi et al. 2006). Low calcitriol levels may persist after transplantation (Uyar et al. 2006; Sprague et al. 2008; Fleseriu and Licata 2007; Tripathi et al. 2008; Querings et al. 2006). Low serum 25-OHD levels were recently reported in nearly half of renal transplant recipients; this may represent improvement from older studies that reported vitamin D deficiency in over 75 % of renal transplant candidates, likely because of greater awareness of vitamin D (Beique et al. 2013). Sclerostin, secreted by osteocytes, is an inhibitor of the Wnt-signaling pathway which leads to decreased bone formation (Bonani et al. 2014). Sclerostin levels tend to be high in patients before renal transplantation. Although sclerostin levels decline within 15 days after transplant, it is unclear whether this is due to increased sclerostin catabolism or

decreased sclerostin secretion, as phosphorus levels normalize (Bonani et al. 2014; Pelletier et al. 2013).

11.3.3 Cardiac Transplantation

The prevalence of osteoporosis in patients awaiting cardiac transplantation ranges from 4 to 23 %(Shane et al. 1997a, 2004; Dolgos et al. 2010; Anijar et al. 1999; Cohen and Shane 2005; Lee et al. 1994; Iqbal et al. 2008). Observational studies, primarily conducted during the 1990s, documented rates of bone loss ranging from 4 to 11 %, with the most rapid losses during the first 3–12 months, with greater losses at the hip than the spine (Stempfle et al. 1998; Shane et al. 2004; Berguer et al. 1994; Cremer et al. 1999; Henderson et al. 1995; Sambrook et al. 1994a; Shane et al. 1997b; Thiebaud et al. 1996; Valimaki et al. 1999a; Van Cleemput et al. 1995). The few longitudinal data after the first year suggest that the rate of bone loss slows or stops in the majority of patients, with partial recovery of bone mass at the spine though not at the hip (Shane et al. 2004; Shane et al. 1997b). More recent studies suggest lower rates of spine and hip bone loss (2–3 %) than previously reported, likely related to lower GC exposure than patients transplanted in the 1990s (Shane et al. 2004, 2012). However, while some GC-sparing protocols are associated with less bone loss, these results are not consistent across studies suggesting factors other than GCs are responsible for posttransplant bone loss (Baraldo et al. 2014).

Observational studies conducted during the 1990s found that approximately one-third of cardiac transplant recipients sustained a fragility fracture during the first 1–3 years after grafting (Shane et al. 1996a; Leidig-Bruckner et al. 2001). Fractures were associated with female gender, lower pretransplant BMD, and higher rates of bone loss after transplantation (Shane et al. 1996a; Leidig-Bruckner et al. 2001). However, many patients who fractured had normal BMD prior to transplant (Shane et al. 1996a; Leidig-Bruckner et al. 2001). In contrast, more recent studies report fracture incidence to be considerably lower than in the past, in the range of 12–14 %(Shane et al. 2004; Kerschan-Schindl et al. 2008). One study compared fracture risk between GC-free protocols, low-dose GC protocols (prednisone ≤ 5 mg daily by the end of the first posttransplant year), and high-dose GC protocols (prednisone > 5 mg daily by the end of the first posttransplant year). At 2 years, there was no difference in fracture incidence among the three groups (1.1 %, 1.5 %, and 2.5 %, respectively) (Crespo Leiro et al. 2012). A recent retrospective study of 105 patients who received a heart transplant between 2005 and 2010 reported that 8.6 % sustained a fragility fracture, with a median time to first fracture of 12 months. A slightly larger proportion of women than men fractured (11.8 % versus 8.0 %). There was a high rate of bisphosphonate use in both fracture and non-fracture groups, 56 % versus 39 %, which may have reduced fracture rates (Hariman et al. 2014).

Early studies reported biochemical evidence of uncoupled bone remodeling (increased resorption and decreased formation) during the first 3–6 months after

heart transplant, with restitution of coupling when glucocorticoid doses are lowered (Shane et al. 1997b; Valimaki et al. 1999a; Sambrook et al. 1994b). Later in the posttransplant period, many studies suggest that bone remodeling is increased (Lee et al. 1994; Thiebaud et al. 1996; Valimaki et al. 1999a; Sambrook et al. 1994b; Glendenning et al. 1999; Guo et al. 1998; Rich et al. 1992; Shane et al. 1993). Vitamin D deficiency is extremely common among heart and liver transplant recipients at the time of transplantation. In one study of patients assessed within the first 1–2 weeks after transplant, 55 % had deficiency with serum 25-OHD levels between 10 and 20 ng/ml, and 16 % had levels < 10 ng/ml (Stein et al. 2009).

11.3.4 Liver Transplantation

Osteoporosis is present in 20–43 % of patients with end-stage liver disease awaiting transplantation (Dolgos et al. 2010; Crosbie et al. 1999; Monegal et al. 1997; Bai et al. 2007; Guichelaar et al. 2006). A recent Spanish study that compared two groups of liver transplant candidates, one evaluated between 1992 and 1993 and the second between 2010 and 2011, found that the prevalence of osteoporosis (22 % versus 30 %, respectively) and vertebral fractures (36 % versus 33 %, respectively) was high and approximately the same in both (Monegal et al. 2013). Vitamin D deficiency is also very common, affecting >80 % of liver transplant candidates (Chaney et al. 2015; Venu et al. 2013). Chronic liver disease, of various etiologies, is associated with low levels of serum RANKL and high levels of OPG, possibly leading to an increased OPG/RANKL ratio, osteoclast inhibition, and a low bone-turnover state (Gatta et al. 2014). In fibrotic liver diseases, the synthesis of type I collagen is markedly increased and thus collagen-related bone-turnover markers do not reflect skeletal turnover in patients with liver disease (Guanabens et al. 1998). Serum osteocalcin and tartrate-resistant acid phosphatase (TRAP) may be more valid markers of bone remodeling activity.

In studies published before 2000 (Leidig-Bruckner et al. 2001; Eastell et al. 1991; Haagsma et al. 1988; Hawkins et al. 1994; Hussaini et al. 1999; Lopez et al. 1992; McDonald et al. 1991; Meys et al. 1994; Navasa et al. 1994; Porayko et al. 1991; Keogh et al. 1999), spine BMD fell by 2–24 %, primarily in the initial few months after liver transplantation, with recovery to levels equal to or even higher than before transplant by 1 year. More recent studies have reported lower rates of bone loss at the femoral neck (Keogh et al. 1999) and no significant bone loss at the spine (Ninkovic et al. 2002)·(Floreani et al. 2001). In a recent cohort study of 201 liver transplant recipients from the Netherlands, the majority treated with predni-sone for at least 6 months and either tacrolimus or cyclosporine, lumbar spine BMD declined by 2.5 % but returned to pretransplant levels by 2 years. In contrast, femoral neck BMD had declined by 6.5 % at 6 months and remained stable thereafter, with no recovery over 5 years of follow-up (Krol et al. 2014a). Lower bone mass and/or higher rates of bone loss after liver transplant have been associated with older age, female gender, cholestatic liver disease, and higher prednisone dose (Smallwood et al. 2005).

In older studies, fracture incidence was extremely high, ranging from 24 to 65 %. Some recent studies suggest that fracture rates are lower (Ninkovic et al. 2002; Kaemmerer et al. 2012). However, in the Netherland cohort study, radiographic vertebral fractures were present in 56 % at screening, 68 % at 6 months, and 71 % at 12 months (Krol et al. 2014a), suggesting that vertebral fractures remain a significant problem (Krol et al. 2014a). Factors that have been associated with increased risk of fracture include male gender (Krol et al. 2014a), primary sclerosing cholangitis (Guichelaar et al. 2006) and alcoholic cirrhosis (Millonig et al. 2005), older age and lower pretransplant BMD (Ninkovic et al. 2002; Monegal et al. 2001b), prevalent pretransplant vertebral fractures, and longer survival (Leidig-Bruckner et al. 2001; Ninkovic et al. 2000).

PTH increases significantly during the first 3–6 months after liver transplant (Floreani et al. 2001; Monegal et al. 2001b; Compston et al. 1996). Serum 25-OHD concentrations are low in recent liver transplant recipients, likely because of disease-related factors such as malabsorption, impaired hepatic 25-hydroxylation of vitamin D, and reduced production of vitamin D-binding protein (Stein et al. 2009). Bone turnover, measured by markers of bone formation (osteocalcin and carboxyterminal peptide of type I collagen) and resorption are higher in liver transplant recipients than in normal controls in most (Haagsma et al. 1988; Abdelhadi et al. 1995; Watson et al. 1990; Valero et al. 1995), though not all studies (Rabinowitz et al. 1992). OPG and RANKL levels are significantly elevated in the first 2 weeks following liver transplant (Fabrega et al. 2006). In 21 patients who underwent tetracycline-labeled bone biopsies before and 3 months after transplantation, low turnover transitioned to a high turnover state (Compston et al. 1996; Vedi et al. 1999).

11.3.5 Lung Transplantation

Osteoporosis is extremely common among patients with end-stage lung disease. In cross-sectional studies, low bone mass and osteoporosis have been documented in 31–86 % of candidates for lung transplantation (Aris et al. 1996, 1998, 2000; Donovan et al. 1998; Ott and Aitken 1998; Shane et al. 1996b; Tschopp et al. 2006; Caplan-Shaw et al. 2006; Jastrzebski et al. 2010). All etiologies appear to be vulnerable. Markedly increased rates of all fractures and severe kyphosis due to vertebral fractures have been reported in adults with cystic fibrosis (Aris et al. 1998; Donovan et al. 1998; Ott and Aitken 1998). Low BMD and osteoporosis are also highly prevalent in patients with emphysema (Aris et al. 1996; Shane et al. 1996b), diffuse parenchymal lung disease (Caplan-Shaw et al. 2006), and primary pulmonary hypertension (Tschopp et al. 2006). The etiology of osteoporosis in patients with end-stage lung disease is multifactorial. In addition to prior GC exposure (Park et al. 1996; Aris et al. 1996; Shane et al. 1996b; Jastrzebski et al. 2010; Wang et al. 2013), low body weight, chronic hypoxemia, tobacco exposure, and chronic infection/inflammation have been implicated. In some studies, BMD correlated with pulmonary vascular resistance, functional measures, and walking distance (Tschopp et al. 2006; Caplan-Shaw et al. 2006). In patients with cystic fibrosis, additional etiologic

factors include calcium malabsorption, hypogonadism, small body size, and vitamin D deficiency (Donovan et al. 1998).

Not surprisingly, therefore, osteoporosis affects a very high proportion of lung transplant recipients. In fact, a population-based cohort study from Taiwan found that those at highest risk for osteoporosis and various types of fracture after solid organ transplant were lung transplant recipients (Yu et al. 2014). Prospective studies have shown that spine and hip BMD declines by 4–5 % during the first year (Ferrari et al. 1996; Spira et al. 2000). An HRpQCT study comparing 58 lung transplant recipients and 60 controls found lung transplant recipients had greater cortical porosity, lower trabecular number and thickness, bone stiffness, and failure load (Fischer et al. 2015). In studies from the 1990s, fracture incidence varied from 11 to 42 %(Spira et al. 2000; Aringer et al. 1998; Rutherford et al. 2005; Shane et al. 1999). Risk factors for fracture and bone loss after lung transplant include female gender; low pretransplant BMD; pretransplant GC therapy; GC dose in some (Spira et al. 2000), but not all studies (Shane et al. 1999); pretransplant fractures; and high bone turnover after transplantation (Wang et al. 2013). In contrast, a retrospective study of patients transplanted between 2005 and 2010 reported a somewhat lower fracture rate of 8.0 %, perhaps because approximately 50 % were receiving bisphosphonates (Hariman et al. 2014).

11.3.6 Bone Marrow Transplantation (BMT)

As in the case of solid organ transplantation, low BMD is common in patients who require BMT. Bone loss may be related both to the underlying disease and to pretransplant myeloablative therapy with alkylating agents and/or total body irradiation, which may precipitate profound and frequently permanent hypogonadism, particularly in women, and may also have toxic effects on bone marrow osteoprogenitor cells (Banfi et al. 2001). Pretransplant exposure to GCs may also contribute. In patients studied after myeloablative chemotherapy but before BMT, osteopenia was present in 24 % and osteoporosis in 4 %(Schulte et al. 2000).

Adverse skeletal effects are more common after allogeneic BMT, in which donor and recipient are not genetically identical, than after autologous BMT, which involves removal and reinfusion of the patient's own stem cells after high-dose myeloablative therapy (Ebeling et al. 1999). After allogeneic BMT, there is a substantial risk of acute or chronic graft-versus-host disease (GVHD), in which donor immune cells react against the recipient. GVHD is typically treated with combinations of high-dose GCs, methotrexate, cyclosporine A, or tacrolimus. Several studies have documented low total body BMD and spine BMD measured by DXA and CT (Kelly et al. 1990; Bhatia et al. 1998; Yao et al. 2008; Nysom et al. 2000; Kauppila et al. 1999; Kerschan-Schindl et al. 2004). Those younger than 18 at transplantation may be more profoundly affected, perhaps because of failure to achieve optimal peak bone mass and smaller bone size (Bhatia et al. 1998, Frisk et al. 2012). Factors associated with low BMD 6 months after BMT include GVHD, GC use, low vitamin D levels, and family history of osteoporosis (Campos et al. 2014). In adult BMT

recipients, hematopoietic stem cell transplantation before age 10 was associated with lower total body and femoral neck BMD than after age 18 (Petryk et al. 2014). Bone mass is low in hypogonadal women after BMT and hormone replacement therapy is associated with significant increases in BMD (Branco et al. 1996; Castaneda et al. 1997).

After BMT, spine bone loss ranges between 2 and 6 %, while FN BMD declines by 6–12 % (Serio et al. 2013; Ebeling 2005; Valimaki et al. 1999b; Kashyap et al. 2000). Duration of GC exposure may be more prognostic than cumulative dose (Serio et al. 2013). While there appears to be little bone loss after the first year (Kauppila et al. 1999), FN bone loss may not be regained. A recent study from the MD Anderson Cancer Center found that 8 % of patients fractured after BMT (Pundole et al. 2015). Risk factors included age over 50, multiple myeloma, solid organ tumors, and autologous BMT (Pundole et al. 2015). Vertebral fractures were slightly more common (53 %) than non-vertebral fractures (47 %) (Pundole et al. 2015), which mostly affected the ribs, upper limbs, and femur (Pundole et al. 2015).

The pathogenesis of post-BMT bone loss is complex. Cellular or cytokine-mediated bone marrow dysfunction may affect bone remodeling and loss after BMT (Lee et al. 2002a). High-dose chemotherapy, total body irradiation, and treatment with GCs and/or CsA may reduce osteoblast differentiation. Colony-forming unit fibroblasts (CFU-f) are reduced for up to 12 years following BMT (Banfi et al. 2001; Tauchmanova et al. 2002). During the first 3 months after BMT, bone formation markers decrease and resorption markers increase (Valimaki et al. 1999b), a pattern consistent with uncoupling of formation from resorption. After 3 months, bone formation markers rebound and elevated turnover persists during the latter half of the year (Kauppila et al. 1999; Valimaki et al. 1999b; Carlson et al. 1994; Withold et al. 1996; Lee et al. 2002b; Kang et al. 2000). Long-term survivors after BMT may have persistent abnormalities in bone turnover and vitamin D (Kananen et al. 2002).

11.4   Evaluation and Management of Osteoporosis in Patients Awaiting Transplantation

Candidates for all types of transplantation should be evaluated so that potentially treatable abnormalities of bone mineral metabolism may be addressed and bone health optimized preoperatively (Table 11.1). BMD of the spine and hip should be measured by DXA and spine x-rays or vertebral fracture analysis (VFA) performed to detect prevalent fractures, which are associated with an increased risk of incident fractures. If pretransplant BMD is low, a thorough evaluation should be performed to detect potentially treatable causes of low bone mass and guide therapy. On a cautionary note, however, one study found no association between BMD and vertebral fractures in OLT recipients suggesting that BMD may not provide a complete radiologic assessment of pretransplant bone health (Krol et al. 2014b). Patients found to have osteoporosis before transplantation should receive treatment, typically antiresorptive therapy with a bisphosphonate. Teriparatide can be considered for patients with very low BMD or fractures if they do not have

Table 11.1 Skeletal evaluation of the candidate for organ transplantation

In all candidates:
Assess risk factors for osteoporosis, including menstrual/menopausal history in women, history of low-trauma fractures
Measure bone densitometry (BMD) of the spine and hip by DXA
Obtain thoracic and lumbar spine radiographs or vertebral fracture analysis by DXA
If BMD testing reveals osteoporosis or if there are prevalent vertebral or non-vertebral fractures:
Serum electrolytes, BUN creatinine, calcium, parathyroid hormone, 25-hydyroxyvitamin D, thyroid function tests (see text)
In men, serum total and/or testosterone, FSH, and LH
Urine for calcium and creatinine

hyperparathyroidism. The pretransplant waiting period is often long enough (1–2 years) for significant improvement in BMD before transplantation. Patients with renal osteodystrophy should be managed in accordance with accepted clinical guidelines (Kidney Disease: Improving Global Outcomes 2009).

11.5 Prevention and Treatment of Transplantation Osteoporosis

As bone loss is most rapid during the first 6–12 months after transplantation and fractures may also occur early, strategies to prevent bone loss should be instituted immediately after transplantation, particularly in patients with low BMD and those who will be on GC therapy (Table 11.2).

The most commonly tested therapies for transplantation osteoporosis include bisphosphonates and active vitamin D analogues. While teriparatide is approved for the treatment of GC-induced osteoporosis with increases in BMD and decreases in non-vertebral fractures (Saag et al. 2009), the only study of teriparatide after organ transplantation found that FN BMD did not decline in kidney transplant patients randomized to teriparatide but decreased significantly in those on placebo (Cejka et al. 2008).

11.5.1 Vitamin D Analogues

Active vitamin D analogues prevent GC-induced decreases in intestinal calcium absorption, reduce secondary hyperparathyroidism, promote differentiation of osteoblast precursors into mature cells, and may potentiate immunosuppressive effects of CsA (Briffa et al. 2003; Lemire 1992; Lemire et al. 1994). Alfacalcidol (1-α-OHD) prevented or attenuated bone loss at the LS and FN (El-Agroudy et al. 2003; De Sevaux et al. 2002; El-Agroudy et al. 2005). Calcitriol (0.5–0.75 ug/day) prevented bone loss at the spine and hip during the first 6 months after heart or lung

Table 11.2 Primary prevention of bone loss in transplant recipients

Measure BMD before or immediately after transplantation and then annually
Utilize the lowest dose of glucocorticoids possible
Consider alternative therapies for rejection
Calcium intake (diet+supplements) of 1000 mg/day both before and after transplantation
Vitamin D intake of 400–1000 IU or as needed to maintain serum 25-OHD concentrations above 30 ng/ml (80 nmol/ml)
Physical rehabilitation program both before and after transplantation
Consider gonadal steroid replacement in hypogonadal men and premenopausal women
Consider pharmacologic therapy in all patients with low bone mass (T score between −1.0 and −2.5) or osteoporosis (T score < −2.5)
Begin antiresorptive therapy, preferably a bisphosphonate, before transplantation in patients with osteoporosis
Begin antiresorptive therapy, preferably a bisphosphonate, immediately after transplantation in patients at high risk for fracture
Osteoporosis (T score < −2.5)
History of fragility fracture
FRAX score > 20 %
Postmenopausal women or men >50 years with osteopenia and no history of fragility fracture with osteopenia who are expected to continue on prednisone for greater than 1 month
Premenopausal women and men <50 years with osteopenia and no history of fragility fracture who are expected to continue on prednisone for greater than 1 month

transplantation (Henderson et al. 2001); those who received it for 24 months sustained significantly less FN bone loss, while those who stopped at 12 months had no evidence of benefit at the FN at 24 months (Sambrook et al. 2000). Calcitriol was as effective as daily alendronate in preventing bone loss after heart transplantation (Cohen et al. 2006b). In one study, daily calcitriol was associated with an increase in BMD at the LS, FN, and forearm during the first year after kidney transplantation (Josephson et al. 2004), while in another, intermittent calcitriol prevented bone loss at the hip but not the spine after kidney transplant (Torres et al. 2004). As hypercalcemia and hypercalciuria may develop rapidly and at any time during therapy with active vitamin D analogues, frequent monitoring of serum and urine calcium is necessary.

11.5.2 Bisphosphonates

Two meta-analyses of bisphosphonate trials in kidney transplant recipients found that bisphosphonates prevented bone loss at the spine and hip (Mitterbauer et al. 2006; Palmer et al. 2005). Similarly, a meta-analysis of randomized controlled trials in diverse transplant types showed that treatment with bisphosphonates improved spine and hip BMD by approximately 3 % on average (Cohen et al. 2011).

Intravenous bisphosphonates consistently prevent bone loss after transplantation (Valero et al. 1995; Aris et al. 2000; Fan et al. 2000, 2003; Garcia-Delgado et al.

1997; Shane et al. 1998; Bianda et al. 2000; Hommann et al. 2002; Grotz et al. 2001; Arlen et al. 2001; Trombetti et al. 2000; Krieg et al. 2001; Haas et al. 2003; Coco et al. 2003; Walsh et al. 2009; Jeon et al. 2013; Okamoto et al. 2014). Repeated doses of intravenous pamidronate prevented spine and hip bone loss in the kidney (Fan et al. 2000, 2003; Coco et al. 2003; Torregrosa et al. 2011), heart (Bianda et al. 2000; Krieg et al. 2001), liver (Pennisi et al. 2007; Monegal et al. 2009), lung (Aris et al. 2000; Trombetti et al. 2000), and bone marrow transplant recipients (Kananen et al. 2005; Grigg et al. 2004). A meta-analysis of six studies (144 kidney transplant patients) found that pamidronate, given 3–7 times at 30–90 mg per dose, was associated with significant reduction of bone loss in the spine without adverse effects on graft function (Wang et al. 2014). Similarly, both zoledronic acid and ibandronate prevent bone loss at 6 and 12 months in recipients of heart (Fahrleitner-Pammer et al. 2009), liver (Hommann et al. 2002; Crawford et al. 2006; Bodingbauer et al. 2007), and kidney (Grotz et al. 2001; Haas et al. 2003; Walsh et al. 2009; Smerud et al. 2012) transplants. Zoledronic acid administered monthly for the first 6 months and at 9 and 12 months after liver transplantation was associated with stable BMD at the spine and reduced losses at the FN compared to controls and was associated with a reduction in vertebral fractures (Bodingbauer et al. 2007). Ibandronate, 2 mg IV every 3 months for 1 year, maintained spine BMD and attenuated hip bone loss after liver transplantation, with a significant reduction in number of fractures (Kaemmerer et al. 2010). In long-term liver transplant recipients, quarterly IV ibandronate and calcitriol were associated with improvements in BMD at the hip and a reduction in vertebral fractures over 3 years compared to an untreated reference group (Wagner et al. 2012).

In two large prospective studies of patients after allogeneic BMT, IV pamidronate prevented bone loss at the spine and ameliorated losses at the hip (Kananen et al. 2005; Grigg et al. 2004). Similarly, IV zoledronic acid (4 mg) given 12 months after grafting and in another study, given every 3 months for 2 years, prevented spine and hip bone loss (Tauchmanova et al. 2005; Hausmann et al. 2012). In a small uncontrolled study, BMD was stable over 3 years after BMT in patients who received zoledronic acid once at transplant and 6 months later (Ganguly et al. 2012). When BMT patients were treated with zoledronic acid, FN BMD increased at 12 months (Lee et al. 2002c; Hari et al. 2013). Similarly, monthly zoledronic acid infusions for the first 3 months after BMT restored BMD at the LS and FN (Serio et al. 2013).

Results with oral bisphosphonates are less compelling. There was no change in BMD in 42 renal transplant patients randomized to risedronate or placebo, although risedronate appeared to preserve BMD in women (Coco et al. 2012). Monthly oral ibandronate (150 mg) or weekly oral risedronate (35 mg) initiated 12 months after kidney transplant provided comparable increases in spine and hip BMD after 1 year (Sanchez-Escuredo et al. 2015). A study of 76 kidney transplant recipients treated with weekly oral alendronate (70 mg) found improvements in lumbar spine BMD both in patients with and without preexisting osteoporosis after 14 months of therapy (Huang et al. 2012). Alendronate reduced bone-turnover markers in 24 kidney transplant recipients after 36 months of treatment (Yamamoto et al. 2013). Kidney

transplant patients treated with alendronate (10 mg daily), calcitriol (0.25 µg daily), and calcium carbonate (2 g daily) had marked increases in spine BMD compared to decreases in those who received only calcium and calcitriol (Kovac et al. 2001). There were similar increases in spine BMD in patients treated with alendronate or risedronate after kidney transplant (Nowacka-Cieciura et al. 2006; Torregrosa et al. 2007; Giannini et al. 2001). Weekly alendronate (70 mg) improved BMD in kidney (Toro et al. 2005) and liver transplant recipients (Atamaz et al. 2006). Risedronate prevented bone loss at the spine but not the hip 12 months after liver transplant (Guadalix et al. 2011). In contrast, monthly oral ibandronate increased spine and hip BMD in 74 liver transplant patients, and fracture rates were relatively low (5.4 %) (Kaemmerer et al. 2012). Both alendronate (10 mg daily) and calcitriol (0.25 µg twice daily) initiated immediately after heart transplant prevented bone loss at the spine and hip compared with a reference group receiving only calcium and vitamin D (Shane et al. 2004); BMD remained stable during the second year after alendronate and calcitriol were discontinued (Cohen et al. 2006a). A single infusion of zoledronic acid (5 mg) or weekly alendronate (70 mg) initiated immediately after heart and liver transplantation prevented bone loss at the hip and, in liver transplant patients, at the spine compared to a reference group that received only calcium and vitamin D (Cohen et al. 2011). In heart transplant patients, spine bone mineral density increased with IV zoledronic acid and decreased on alendronate (Cohen et al. 2011). In BMT patients, risedronate started 12 months after BMT improved LS BMD and prevented loss at the FN (Tauchmanova et al. 2003).

Although fracture is a very important clinical outcome, few studies have had adequate power to detect differences in fracture. A meta-analysis of 11 randomized controlled clinical trials showed that treatment with either bisphosphonates or vitamin D analogues significantly reduced the number of subjects with fracture by 50 % and number of vertebral fractures by 76 %. When vitamin D analogue trials were excluded and bisphosphonate trials examined separately, there was a significant 47 % reduction in number of subjects with fractures but the 66 % reduction in vertebral fractures was not significant (Cohen et al. 2011). In our opinion, bisphosphonates represent the most promising approach to the prevention of transplantation osteoporosis, but data on fracture prevention is needed.

11.6   Summary and Conclusions

The prevalence of osteoporosis among candidates for solid organ and bone marrow transplantation is high. During the 1990s, prospective longitudinal studies demonstrated rapid bone loss and high fracture rates, particularly during the first posttransplant year. More recent studies suggest that rates of bone loss and fracture are considerably lower than in the past, although rates remain unacceptably high. All patients should be evaluated before transplantation and receive treatment for prevalent osteoporosis, if present. Primary prevention therapy should be initiated immediately after transplantation in patients with low BMD, advanced age, or other significant risk factors, as the most rapid bone loss occurs in the first few months after grafting.

Table 11.3 Management of the long-term organ transplant recipient

In all patients:
Assess risk factors for osteoporosis
BMD of the spine and hip by DXA
Thoracic and lumbar spine radiographs
Calcium intake of 1000 mg/day both before and after transplantation
Vitamin D intake of 400–1000 IU or as needed to maintain serum 25-OHD concentrations above 30 ng/ml (80 nmol/ml)
Physical rehabilitation program
If BMD testing reveals osteoporosis or there are prevalent vertebral fractures:
Serum electrolytes, BUN creatinine, calcium, parathyroid hormone, 25-hydroxyvitamin D, thyroid function tests
In men, serum total and/or testosterone, FSH, and LH
Urine for calcium and creatinine
Replace gonadal steroids (in men and hypogonadal women, if appropriate)
Begin antiresorptive therapy, preferably a bisphosphonate
These recommendations should not be applied to kidney transplant recipients, in whom the risk of the adynamic bone lesion is high and benefits of bisphosphonates are controversial

Long-term transplant recipients should be monitored and treated for bone disease as well (Table 11.3). At present, bisphosphonates are the most consistently effective agents for prevention and treatment of bone loss in organ transplant recipients. In the future, the use of denosumab or the introduction of newer, bone-sparing immunosuppressive agents may further reduce rates of bone loss after transplant. It is hoped that these advances will further reduce morbidity from transplantation osteoporosis.

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