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Review Article

Bone disease following solid organ transplantation: A narrative review and recommendations for management from The European Calcified Tissue Society

Athanasios D. Anastasilakis[a,1], Elena Tsourdi[b,c,1], Polyzois Makras[d], Stergios A. Polyzos[e], Christian Meier[f], Eugene V. McCloskey[g,h], Jessica Pepe[i], M. Carola Zillikens[j,*]

[a] Department of Endocrinology, 424 General Military Hospital, 54638 Thessaloniki, Greece
[b] Department of Medicine III, Technische Universität Dresden Medical Center, Dresden, Germany
[c] Center for Healthy Aging, Technische Universität Dresden Medical Center, Dresden, Germany
[d] Department of Endocrinology and Diabetes, 251 Hellenic Force & VA General Hospital, Athens, Greece
[e] First Department of Pharmacology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece
[f] Division of Endocrinology, Diabetology and Metabolism, University Hospital and University of Basel, Switzerland
[g] Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, UK
[h] Centre for Integrated research in Musculoskeletal Ageing (CIMA), Mellanby Centre for Bone Research, University of Sheffield, Sheffield, UK
[i] Department of Internal Medicine and Medical Disciplines, "Sapienza" University, Rome, Italy
[j] Bone Center, Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands

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ABSTRACT

Introduction: Solid organ transplantation is an established therapy for end-stage organ failure. Both pre-transplantation bone disease and immunosuppressive regimens result in rapid bone loss and increased fracture rates.
Methods: The European Calcified Tissue Society (ECTS) formed a working group to perform a systematic review of existing literature on the consequences of end-stage kidney, liver, heart, and lung disease on bone health. Moreover, we assessed the characteristics of post-transplant bone disease and the skeletal effects of immunosuppressive agents and aimed to provide recommendations for the prevention and treatment of transplantation-related osteoporosis.
Results: Characteristics of bone disease may differ depending on the organ that fails, but patients awaiting solid organ transplantation frequently depict a wide spectrum of bone and mineral abnormalities. Common features are a decreased bone mass and impaired bone strength with consequent high fracture risk, all of which are aggravated in the early post-transplantation period.
Conclusion: Both the underlying disease leading to end-stage organ failure and the immunosuppression regimens implemented after successful organ transplantation have detrimental effects on bone mass, quality and strength. Given existing ample data confirming the high frequency of bone disease in patients awaiting solid organ transplantation, we recommend that all transplant candidates should be assessed for osteoporosis and fracture risk and, if indicated, treated before and after transplantation. Since bone loss in the early post-transplantation period occurs in virtually all solid organ recipients and is associated with glucocorticoid administration, the goal should be to use the lowest possible dose and to taper and withdraw glucocorticoids as early as possible.

1. Introduction

Organ failure is associated with adverse effects on bone mass, quality and strength, and an increased risk for fractures [1]. Organ transplantation improves the recipient's quality of life, but bone health remains impaired and fracture risk high, at least during the first years post-transplant. Although, bone disease has unique characteristics, depending on the affected organ, a common aggravating factor for the post-transplant period is the use of immunosuppressants, especially glucocorticoids (GCs). The European Calcified Tissue Society (ECTS) formed a working group to perform a systematic review of existing literature on the post-transplant bone disease and its management and

* Corresponding author at: Department of Internal Medicine, Erasmus Medical Center, 's-Gravendijkwal 230, 3015 CE Rotterdam, the Netherlands.
E-mail address: m.c.zillikens@erasmusmc.nl (M.C. Zillikens).
[1] Authors contributed equally.

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provide guidance for the prevention and treatment of transplantation-related osteoporosis.

2. Literature search

A computerized literature search was performed in PubMed (last update: April 18, 2019). Search was not limited by publication time or language. Medical Subject Heading (MeSH) database was used as a terminological search filter in combination with methodological search filters (Appendix 1). The literature search was extended by "hand searching" in the "related citations" links of all included articles in PubMed (first 40 articles per included article, after sorting according to the relevance), and the references of all included articles.

3. The effects of post-transplant immunosuppressive agents on the skeleton

Immunosuppressive agents (IA) affect bone metabolism [1–3]. Their effects further aggravate the pre-transplant bone disorder which is partly due to the original disease and partly a result of additional risk factors such as smoking, decreased physical activity, hypoxia and, where necessary, previous use of GCs. As a result, the evaluation of IA's direct effects on the skeleton can be a very complicated task [4,5]. In fact, it seems that the more debilitating the underlying disease before transplantation, the more severe the bone disorder following transplantation, while IAs may also exert additional detrimental long-term consequences [1]. The effect of GCs and other IAs on post-transplant bone homeostasis and fracture risk is discussed in this section.

3.1. Glucocorticoids

GCs constitute the mainstay of post-transplant immunosuppressive intervention. In the past, GCs were administered in initially high doses which were gradually tapered over a long time. Both the initial dose and the weaning period are nowadays substantially reduced [6]. However, doses are frequently increased during rejection episodes or graft versus host disease.

GCs exert multiple effects on bone metabolism, and GC-induced osteoporosis (GIOP) is the most common form of secondary osteoporosis [7,8]. The pathogenesis of bone loss following the administration of GCs is multifactorial including both direct and indirect effects on osseous tissue and results in a reduction of bone mass and an overall deterioration of bone strength [9,10]. Specifically within the transplantation period, the higher GC-induced rate of bone loss is observed during the first 3 to 12 months following transplant with trabecular skeletal sites being primarily affected [6]. This rapid bone mineral density (BMD) decline is initially caused by excessive bone resorption which is later followed by impaired bone formation. At the cellular level GCs stimulate the production of receptor activator of NF-kappa B ligand (RANKL) by the osteoblasts while simultaneously reducing its decoy receptor, namely osteoprotegerin (OPG), thus enhancing the differentiation, activation, and survival of osteoclasts [9,10]. The prolongation of osteoclasts' life span caused by the induction of macrophage colony stimulation factor (M-CSF) by GCs further contributes to the early phase of rapid bone loss [11]. However, osteoblasts are probably the most severely affected bone cells by GCs and both their number and function are profoundly reduced leading to substantially impaired bone formation [9,10]. GCs administration also inhibits the function of mature osteoblasts and suppress the synthesis of type I collagen as well as insulin-like growth factors (IGFs), agents that enhances bone formation [6]. Inhibition of Wingless (Wnt)-β-catenin signaling, and overexpression of Notch receptors enhance the apoptosis of both osteoblasts and osteocytes by caspase 3 activation [11]. Specifically, the detrimental effect of GCs on osteocytes might contribute to the disproportionate bone strength reduction in relation to BMD loss, as the failure of the osteocytic network to detect disrupted tissue leads to defective replacement of damaged bone [12,13].

Furthermore, GCs oppose vitamin D action thus reducing intestinal calcium absorption and inhibiting renal tubular calcium reabsorption; calcium metabolism is further deregulated by the GC-induced inhibition of growth hormone, IGF-1, gonadotropins, and the alteration of parathyroid hormone (PTH) secretory dynamics [14–16]. Although the net effect on bone turnover markers (BTM) in patients under chronic GCs treatment is congruent with reduced bone formation [15], an enhanced bone remodeling with increased bone resorption markers usually characterizes the immediate post-transplantation period with secondary hyperparathyroidism playing a crucial role in this high turnover state [6]. Secondary hyperparathyroidism in this setting, may be aggravated by low vitamin D levels usually seen in these patients before transplantation [17]. In addition, negative effects of GCs on muscle and sex hormone levels may contribute to the increased risk for fractures through indirect negative effects on bone, muscle strength and balance.

The current therapeutic trend favors the usage of the lowest possible GCs dose for graft survival. Both calcineurin inhibitors and other IAs have limited the use of GCs [6], although GIOP has even been reported with 7.5–10 mg of daily prednisolone [18,19] or early withdrawal protocols [20]. Although pathophysiologically an overall reduction of the total GCs received after transplantation seems beneficial in terms of skeletal health, prospective studies are needed to prove this hypothesis and evaluate the long-term effects of this therapeutic approach [6].

3.2. Calcineurin inhibitors: cyclosporine and tacrolimus

Cyclosporine and tacrolimus bind with high affinity to cytoplasmic proteins. They impair the transcription of interleukin(IL)-2 and other cytokines such as tumor necrosis factor (TNF)-α, IL-3, IL-4, and interferon gamma (IFN-γ) in T lymphocytes through the selective inhibition of calcineurin, and constitute the mainstay of immunosuppressive treatment following solid organ transplantation [21]. They lack significant myelosuppresive activity [22], however their long term use can be challenging due to renal toxicity and induction of hypertension through renal vasoconstriction and sodium retention [23].

It was originally reported that cyclosporine reduces bone resorption and inhibits the activity of osteoclasts while simultaneously increasing the osteoblastic function [24,25]. Conversely, results from kidney transplant recipients (KTRs) support the notion that bone loss could be avoided with a post-transplant regimen including cyclosporine but not GCs [26–28] leading to a decreased fracture rate [29]. Significant BMD reduction was also initially reported among transplant patients treated with tacrolimus [30,31]. However, tacrolimus-based regimens may limit GCs use and overall cause a more modest BMD reduction than cyclosporine [6,32,33]. Furthermore, a subsequent study in rats treated with tacrolimus reported increased bone volume and decreased osteoclast number [34]. Recently a study in rodents compared a one-month use of cyclosporine (15 mg/kg) versus tacrolimus (1.5 mg/kg) [28]. Although the doses used were significantly higher than those of the usual human regimens (4–10 mg/kg for cyclosporine and 0.1–0.2 mg/kg for tacrolimus), cyclosporine increased both bone formation and bone resorption, leading to a high-turnover bone loss, while tacrolimus enhanced bone resorption without affecting bone formation, but also resulted in bone loss [28]. In any case, given that at least in pre-clinical models calcineurin inhibitors exert a dose-dependent effect on bone [35], BMD monitoring should be recommended to patients receiving those agents.

3.3. Mammalian target of rapamycin inhibitors (mTORi): sirolimus and everolimus

Sirolimus is a macrocyclic triene antibiotic that was originally developed as an antifungal agent but later proved to possess significant antiproliferative and immunosuppressive properties. Everolimus is also a macrolide immunosuppressive agent and a sirolimus analog. Both

agents inhibit the activity of the mammalian target of rapamycin (mTOR) [36]. The main difference with the previous IAs, namely cyclosporine and tacrolimus, is that the former inhibit the production of cytokines while sirolimus and everolimus inhibit the response of both T- and B-lymphocytes to cytokines [37].

Next to the anticancer effects, preclinical studies suggested potential beneficial consequences of mTOR inhibition on bone [38]. Specifically, mTOR inhibition led to an upregulation of OPG in bone marrow cells [39] and a substantial decrease of cathepsin K mRNA expression and protein concentrations in human osteoclasts [40]. In addition, animal models have also suggested that mTOR inhibition decreases bone resorption, while osteoblast differentiation was adversely affected at high mTORi concentrations [40].

Clinical data regarding the effect of mTOR inhibition on bone derive from phase III oncological trials. Specifically, BTM data suggest a suppressive effect of everolimus on bone turnover irrespective of previous bisphosphonate (BP) therapy or the presence of bone metastases [41]. Additionally, in clinical studies among KTRs, sirolimus-based immunosuppression was associated with reduced BTM [42], and was shown to inhibit osteoclast formation in vivo and in vitro [43] in direct comparisons with calcineurin inhibitors.

Although both histomorphometric and prospective clinical studies with fracture endpoints are warranted to further clarify the clinical effects of mTORi on the skeleton, current limited data suggest that immunosuppression with these agents may be beneficial for transplant patients at high risk for osteoporosis while concomitantly reducing the need for GCs.

3.4. Other immunosuppressive agents

Mycophenolic acid (MPA) is an inhibitor of B- and T-lymphocyte proliferation and antibody production and has been widely used as a GC sparing agent among transplant patients during the last 4 decades [44]; it is available in two formulations: mycophenolate mefotil (MMF) which is a prodrug improving the bioavailability of MPA, and enteric coated mycophenolate sodium which has significantly less gastrointestinal adverse events (AEs). Dose dependent bone marrow suppression is frequently observed. Azathioprine is another IA used for the prevention of organ transplant rejection, acting as an antagonist of purine metabolism in order to decrease the number of B- and T-lymphocytes, immunoglobulin synthesis, and ILs secretion [45]. Azathioprine is the prodrug of 6-mercaptopurine which is the principal metabolite. Bone marrow suppression can be also observed with these IAs.

Limited data exist regarding possible effects of these agents on bone fragility [6]. Pending further studies, an overall indirect protective effect of these agents can be assumed, primarily through the limitation of concomitant GCs administration.

4. Different types of transplantation

4.1. Renal transplantation

4.1.1. Bone disease in renal insufficiency

Chronic kidney disease (CKD) is characterized by an imbalance in bone remodeling in favor of bone resorption. Uremic environment impairs osteogenic differentiation of bone marrow mesenchymal cells while RANKL is upregulated [46]. Bone disease in this setting is a unique entity, which comprises a large spectrum of clinical phenotypes, all associated with a high risk of fracture, which is classically named as renal osteodystrophy and more recently as mineral and bone disorder (MBD) associated with CKD (CKD-MBD), a term which, besides bone disorder, also includes biochemical and soft tissue abnormalities [47,48].

There is a gradual increase of fracture risk as renal disease progresses, being several-fold higher at end-stage kidney disease (ESKD) [47]. According to the Kidney Disease: Improving Global Outcomes (KDIGO) Working Group's most recent guidelines, systematic BMD measurement is recommended in CKD patients [47]. CKD patients and especially those on dialysis patients have increased risk of fractures and death [47,48]. In CKD-MBD bone loss is predominantly of cortical origin and is highly associated with peripheral fractures. Thus, the risk of hip fracture is high among dialysis patients, especially in Caucasian and female patients, and is associated with an increased mortality risk [48]. The augmented fracture risk derives from a combination of classic osteoporosis risk factors with those associated with CKD.

The optimal pharmacological management of CKD-MBD as well as the timing of initiating intervention are ill-defined. The 2017 KDIGO guidelines [47] recommend that in CKD stage 3 to 5 patients with biochemical abnormalities of bone and mineral homeostasis and low BMD or fragility fractures, a follow-up of 6 to 12 months after the correction of mineral disorders should precede the initiation of a specific antifracture therapy, with possible consideration of a bone biopsy. The European Calcified Tissue Society and the European Renal Association of Nephrology Dialysis and Transplantation have proposed that patients with a low BMD without fractures should not be treated as no trial shows any evidence of antifracture efficacy [48].

Most antiosteoporotic treatments are contraindicated in patients with an eGFR $<$ 30 ml/min. There is some evidence that BPs increase BMD but the respective studies did not have sufficient power to show a statistically significant reduction in fracture risk [49]. In a subgroup of stage 4 CKD patients from its pivotal trial, denosumab achieved BMD increases that were comparable with the rest of the study population [50]. However, caution and adequate calcium/vitamin D supplementation is warranted in these patients due to the increased risk of developing severe hypocalcemia. In another study, both denosumab and alendronate treatment improved BMD at the lumbar spine (LS), reduced BTM, and appeared to be safe in hemodialysis patients with osteoporosis [51]. The effect of denosumab on fracture risk in CKD patients is yet unknown.

4.1.2. Evaluating fracture risk

The high fracture risk derives from the combination of CKD-induced changes in bone and mineral metabolism and the classic risk factors of osteoporosis observed in the non-CKD population including higher age, female sex, medical history of fracture, diabetes, and GCs use among others [48].

The association of fracture risk with clinical risk factors assessed by the Fracture Risk Assessment Tool (FRAX) in addition to BMD could be applied in the setting of non-dialysis CKD [52].

CKD patients frequently have scoliosis, osteoarthritis at the LS, and/or vascular or joint calcifications, which may overestimate LS BMD [48]. Spine radiographs could be used to identify presence of these conditions and allow a more precise evaluation of BMD results, and additionally, reveal possible vertebral fractures. Vertebral fracture assessment (VFA) by DXA could also be used as a screening tool for vertebral fractures. However, BMD has a good predictive value for risk of fracture in CKD stages 3 to 5 according to recent cohort studies [53–55]. Furthermore, in a recent study, BMD assessed by dual X-ray absorptiometry (DXA) was not inferior to cortical porosity assessed by high-resolution peripheral computed tomography (HR-pQCT) in identifying ESKD patients with prevalent fragility fracture [56].

Trabecular Bone Score (TBS), a gray-level measurement of bone texture derived from lumbar spine DXA images that is correlated with bone microarchitecture, can be used in clinical practice to improve fracture risk prediction in both ESKD [57,58] and kidney transplant recipients (KTRs) [57,59,60].

BTM were negatively associated with volumetric hip BMD, but not with prevalent fractures in ESKD patients [61]. However, BTM have important limitations in this setting, including high biological variability, retention with worsening kidney disease, pre-analytical issues, and inter-assay variability [62]. Promising new biomarkers that could

serve as surrogates of bone fragility, such as sclerostin or fibroblast growth factor 23 (FGF-23) are yet far from being established [48]. Thus, histomorphometric analysis of the bone biopsy remains the gold standard for the diagnosis and classification of mineral and bone disease (MBD) in CKD patients [63]. However, it is difficult to be performed in everyday clinical practice. Bone-specific alkaline phosphatase (BSAP), procollagen type 1 N-terminal propeptide (P1NP) and tartrate-resistant acid phosphatase could discriminate low from non-low bone turnover [64]. Despite its poor diagnostic accuracy for low bone turnover, PTH can discriminate high bone turnover with accuracy similar to that of the other biomarkers, including C-terminal cross-linking telopeptide of type 1 collagen (CTX) [64]. PTH values below 150 pg/ml, indicative of adynamic bone disease, or above 600 pg/ml, indicative of high-turnover hyperparathyroid bone disease, are associated with increased fracture rates [48]. The combination of BSAP with PTH has been shown to discriminate low from non-low bone turnover and high from non-high bone turnover in dialysis patients [65]. The achievement of serum levels of 25-hydroxyvitamin D (25OHD) above 50 nmol/l (20 ng/ml) is recommended for CKD patients to reduce a high PTH level, which is associated with skeletal fractures [48]. Optimal control of PTH also improves bone mineralization and lowers circulating BTM [48].

4.1.3. Post–transplant bone disease

A wide spectrum of bone and mineral abnormalities, including hypophosphatemia, hypercalcemia, hyperparathyroidism, osteomalacia, osteopenia, and osteoporosis are commonly observed in the post-transplant period and bone disease is not uniformly improved post-transplantation [66].

Increased fracture rates are observed in KTRs compared with the general population [67]. After a mean follow-up of 8.5 years 44% of KTRs sustained a fracture [68]. Fractures may affect appendicular sites more commonly than the axial skeleton [69,70]. Risk factors include general factors such as age and female sex, declining BMD and transplant-specific factors such as diabetes, dialysis duration, older donor age, immunosuppression and CKD-MBD [48,67,71]. Early GCs withdrawal has been recently associated with a significant reduction (31%) of fracture risk and fracture-induced hospitalization among patients following renal transplantation [29].

Bone loss in the first post-transplant year, and especially during the first three to six months, has been well documented [72–78] and is more prominent in areas rich in trabecular bone as in vertebrae [72,79] and in the trabecular sites of the peripheral skeleton [70]. Increased doses of GCs and cyclosporin during the first months post-transplant probably play a role [80]. Bone loss ranges from 4 to 10% at the LS and 5 to 8% at the hip [81] although more recent studies report a more modest bone loss [29,78,82,83] or even no loss [70], possibly because of a lower use of GCs and an increased use of calcium and vitamin D supplementation. Nevertheless, losses of this magnitude are substantially higher than the 1.7% annual rate of LS BMD decline observed in postmenopausal women [84]. Lower body weight, older age, lower glomerular filtration rate (GFR), GC treatment and pre-transplantation diabetes have been associated with lower BMD [85]. BMD values are associated with fracture rates [86], although not as strongly as in patients with primary osteoporosis [87]. While BMD has been reported to predict incident fractures, PTH or BTMs at the time of transplantation did not improve the predictive value of BMD [86]. Most studies report no deterioration of BMD beyond the first year post-transplantation [88,89] although a decrease [72,90] and increase [91] have also been reported. Long-term (> 10 years) post-transplantation, KTRs continued to have lower BMD at the LS, total hip (TH) and femoral neck (FN) compared to healthy controls, but trabecular microarchitecture and bone mechanical properties assessed by TBS and tibial microindentation, respectively, did not significantly differ [92]. On the contrary, impaired trabecular architecture as assessed by QCT had been reported in earlier [79,93] and a later [70] study.

Persistent secondary hyperparathyroidism is an additional risk factor for bone loss in KTRs compared to other organ transplant recipients [94]. Elevated baseline levels of PTH and phosphate, as well as low calcitriol [1,25$(OH)_2$D] and 25OHD values improve post-transplant [72,76,95,96]. Bone turnover decreases regardless of the use of antiresorptive agents [70,76,96] or even teriparatide [95] while BMD may increase even without treatment [70,97]. However, post-transplant bone disease is frequently a high bone turnover state characterized by relatively high bone resorption markers and PTH levels [73] regardless of the administration of BPs [96]. The fact that patients after kidney transplantation may need higher PTH levels in order to maintain bone normal bone turnover could imply a degree of resistance to PTH [98]. KTRs develop low bone turnover with time [99]. High prevalence of low-turnover or adynamic bone disease with and without mineralization defect has been reported in KTRs [100], raising concerns that BPs, by depressing bone turnover, may worsen or initiate adynamic bone disease in this setting [101]. Such findings were reported with pamidronate [102] but not with risedronate [103] or zoledronic acid [70].

Bone biopsies performed 6 to 12 months after transplantation demonstrated reduced bone turnover and impaired mineralization in a considerable number of patients [72,79,102,104]. Thus, early post-transplant bone loss appears to be due to increased bone resorption as well as persistent or newly developed low-turnover renal osteodystrophy [95]. Post-transplant histomorphometry suggests reduced trabecular number and increased trabecular separation [70,79] with an improvement in cortical thickness and porosity [70]. Increased mineral apposition rate, and delayed mineralization, as well as higher osteoid surface compared with the controls has been reported in some [79], but not in all studies [70].

The interpretation of conventional laboratory tests, imaging, and other fracture risk assessment tools should be made with caution as they are not standardized in the post-transplant setting [66].

4.1.4. Preventing and managing bone disease post-transplantation

Calcitriol and alfacalcidol, several BPs (clodronate, alendronate, risedronate, pamidronate, ibandronate, zoledronic acid),either orally or intravenously, in reduced and standard doses as well as with different administration frequency, as well as denosumab and even teriparatide have been evaluated regarding their efficacy to manage bone disease in KTRs.

All randomized controlled trials (RCTs) (Table 1) were underpowered to determine efficacy on fracture risk reduction and reported fractures were captured as adverse events or not reported at all. Therefore, the efficacy of agents administered is based on their effect on BMD as a surrogate marker of bone strength. However, and despite the preservation or increase of BMD with antiresorptives in most studies (Table 1), their anti-fracture efficacy in KTRs remains an area of controversy [83,105]. Besides areal BMD as assessed by DXA [82], TBS [106] and volumetric BMD was also reported to improve with denosumab [82]. On the other hand, trabecular bone loss was only partially attenuated while trabecular connectivity was not influenced by zoledronic acid [70]. Lower initial BMD, higher levels of BTM, and an earlier initiation of BPs have been associated with a better response to therapy interpreted as greater BMD increases [78,85]. In the sole study evaluating teriparatide, early post-transplantation treatment for 6 months did not improve bone turnover, BMD or mineralization [95]. Studies assessing denosumab in KTRs, reported a BMD increase at all sites [82,107], with a magnitude comparable to that reported in postmenopausal women with osteoporosis [82]. Increased risk for urinary tract infections, mainly cystitis, were reported in the same study [82].

Several meta-analyses have aimed to address bone effects of anti-osteoporotic agents, primarily BPs, in KTRs. Nevertheless, the lack of robustness and the heterogeneity among selected studies could have possibly affected the conclusions of these meta-analyses. Toth-Manikowski et al. analyzed 12 RCTs (621 patients) and reported that BPs administration for > 6 months improved BMD at the LS and FN by

Table 1
Randomized controlled trials using active treatment regimens for prevention of bone loss after renal transplantation.

Reference	Patients (active/ control)	Duration (mo)	Treatment regimen	Control regimen	Findings summary
Grotz 1998 [113]	46 (31/15)	12	CLO 800 mg/d *or* Calcitonin 200 IU/d for 2 w every 3 mo plus calcium 500 mg/d	Calcium 500 mg/d	*BMD:*change at LS (4.6 vs. 3.2 vs. 1.8%) and at FN (−1.1 vs. 2.5 vs. −0.8%) in the CLO vs. Calcitonin vs. controls (p = NS between groups) *Fractures:* NR
Fan 2000 [114]	26 (14/12)	12	PAM i.v. 0.5 mg/kg before and 1 mo after Tx	Placebo	*BMD:* maintained with PAM while decreased in controls at both LS and FN *Fractures:* NR
Nam 2000 [218]	50 (15/15/20)	12	PAM i.v. 30 mg every 4w plus calcium 500 mg/d *OR* calcitriol 0.5 μg/d plus calcium 500 mg/d	calcium 500 mg/d	*BMD:* increased with PAM while decreased in calcitriol and control group at both LS (+2.6 vs. −2.2 vs. −8.2) and FN (+1.9 vs. −1.4 vs. −5.1). *Fractures:* NR
Giannni 2001 [219]	40 (20/20)	12	ALN 10 mg/d plus calcitriol 0.5 μg/d plus calcium carbonate 500 mg/d	Calcitriol 0.5 μg/d plus calcium carbonate 500 mg/d	*BMD:* increase 5.0% at LS, 4.5% at FN, and 3.9% at TH. *Fractures:* NR
Grotz 2001 [115]	72 (36/36)	12	IBN i.v. 1 mg before and 2 mg at 3,6,9 mo post-Tx plus calcium 500 mg/d if inadequate dietary intake	NR	*BMD:* maintained with IBN while decreased in controls at both LS (−0,9 vs. −6.5%) and FN (+0,5 vs. −7.7%). *Fractures:* no difference (70% less vertebral deformities and 53% less height loss with IBN).
Koc 2002 [220]	24 (8/8/8)	12	ALN 10 mg/d plus elemental calcium 1000 mg/d	Calcitriol 0.5 μg/d plus elemental calcium 1000 mg/d (Calcitriol group) OR elemental calcium 1000 mg/d (Control group)	*BMD:* increase at LS and FN in the ALN and calcitriol group vs. control group (8.2 vs. 6.9 vs. 0.1% and 9.3 vs. 8.5 vs. 2.0%, respectively). *Fractures:* NR
De Sevaux 2002 [74]	111 (65/46)	6	Alfacalcidol 0.25 μg/d plus elemental calcium 1000 mg/d	No Rx	*BMD:* lesser decrease at LS (−2.6 vs. −5.0%) and FN (−0,2 vs. −4.0%). *Fractures:* 2 pts. with multiple VFs in Control group
Coco 2003 [102]	59 (31/28)	12	PAM i.v. 60 mg at baseline and 30 mg at 1,2,3,6 mo after Tx plus calcium carbonate and calcitriol	Calcium carbonate and calcitriol	*BMD:* stable at LS in PAM group vs. decline in Control group at 6mo (−0.63 vs. −4.6%) and 12mo (−0.39 vs. −5.81%). Stable at FN in both groups at 6 and 12 mo. *Fractures:* 1 vertebral in PAM – 2 in Controls. No hip fractures. *Biopsies:* stable cancellous bone volume and trabecular thickness in PAM (vs. loss in Controls). Decreased erosion depth and adynamic bone disease in PAM
Haas 2003 [104]	20 (10/10)	6	ZOL i.v. 4 mg at 2w and 3 mo post-Tx plus calcium citrate 1000 mg/d	Placebo plus calcium citrate 1000 mg/d	*BMD:* increase at LS, no change at FN (vs. decrease at both LS and FN in the placebo). *Fractures:* NR. *Biopsies:*increased trabecular bone mineralization
Jeffery 2003 [85]	97 (46/51)	12	ALN 10 mg/d plus calcium carbonate 500 mg/d	Calcitriol 0.25 μg/d plus calcium carbonate 500 mg/d	*BMD:* increase at LS and FN with ALN (4.2% and 3.3%, respectively) and calcitriol (2.0% and 3.3%, respectively). No difference at the LS and FN between groups ($p = 0.082$ and $p = 0.959$, respectively). *Fractures:* NR.
El-Agroudy 2005 [112]	60 (15/15/15/ 15)	12	ALN 10 mg/d *OR* calcitonin 200 IU qod *OR* alfacalcidol 0.5 μg/d (plus calcium carbonate 500 mg/d for all groups)	Calcium carbonate 500 mg/d	*BMD:* % changes in ALN vs. calcitonin vs. alfacalcidol vs.controls at LS (+0.8 vs. +1.7 vs. +2.1 vs. −3.2%), at FN (+0.6 vs. +1.6 vs. +1.8 vs. -3.8%) and at forearm (+1.9 vs. +2.6 vs. +3.2 vs. −1.8%). *Fractures:*NR
Nayak 2007 [75]	50 (27/23)	6	ALN 35 mg/w plus calcium 1000 mg/d and vitamin D supplements	Calcium (1000 mg/d) and vitamin D supplements	*BMD:* both groups significant loss at LS and TH at 3 mo. ALN group restored BMD at 6 mo while in control group further declined. *Fractures:* NR
Cejka 2008 [95]	24 (12/12/)	6	TPTD 20 μg/d plus calcium 1200 mg/d and vitamin D 800 IU/d	Placebo plus calcium 1200 mg/d and vitamin D 800 IU/d	*BMD:* unchanged at FN and radius at 6mo in both groups. Decreased at FN in placebo while preserved with TPTD. *Fractures:* NR. *Biopsies:* bone volume and mineralization unchanged in both groups
Lan 2008 [221]	46	6	ALN 70 mg/w plus calcium carbonate 800 mg/d and calcitriol 0.25 μg/d	Calcium carbonate (800 mg/d) and calcitriol (0.25 μg/d)	*BMD:*increase at FN in ALN group vs. stable in Controls. Increaseat LS in both groups (p = NS). *Fractures:* NR
Trabulus 2008 [222]		12		No Rx	

(*continued on next page*)

Table 1 (*continued*)

Reference	Patients (active/ control)	Duration (mo)	Treatment regimen	Control regimen	Findings summary
	59 (17/12/21/ 9)		ALN 10 mg/d plus alfacalcidol 0.5 μg/d *OR* ALN 10 mg/d *OR* alfacalcidol 0.5 μg/d		*BMD:* greater increase in ALN + alfacalcidol group vs ALN vs. alfacalcidol vs. controls at LS (7.9 vs. 4.4 vs. 0.7 vs. 0.1%) and FN (8.0 vs. 6.5 vs. −1.8 vs. −2.1%). *Fractures:* no fractures at any group.
Walsh 2009 [76]	93 (46/47)	24	PAM i.v. 1 mg/kg at baseline and 1, 4, 8, 12 mo after Tx plus calcium carbonate 500 mg/d and vitamin D 400 IU/d	Calcium carbonate 500 mg/d and vitamin D 400 IU/d	*BMD:* increased at 12mo at LS (+2.1%) in PAM while decreased (−5.7%) in Control group. Unchanged at 12mo at TH and FN (−0.4 and −0.2%, respectively) in PAM while decreased (−4.4 and −2.6%, respectively) in Control group. At 24 mo BMD further increased or stabilized in PAM group while further declined in Control group. *Fractures:*lower fracture rate in PAM group (2 vs. 6 at 24mo; 3.3 vs. 6.4% per year, p = NS)
Torregrosa 2010 [77]	101 (52/49)	12	RIS 35 mg/w plus calcium carbonate 1500 mg/d and vitamin D 400 IU/d	Calcium carbonate 1500 mg/d and vitamin D 400 IU/d	*BMD:* stable at both LS and FN in RIS group vs. decline in control group (NS decline at 6mo in both groups - restored at 12 mo in RIS group while further declined in control group). *Fractures:* 4 VFs with RIS vs. 6 VFs in controls (p = NS). *Other:* no difference in vascular calcifications
Omidvar 2011 [223]	40 (20/20)	6	PAM i.v. 90 mg *OR* ALN 70 mg/w	–	*BMD:* stable with both PAM and ALN at LS (−0.50 vs. −0.64%, $p = 0.5$) and decreased with both at FN (−1.42 vs. −2.03%, $p = 0.003$). *Fractures:* NR
Torregrosa 2011 [96]	29 (19/10)	12	PAM i.v. 30 mg at and 3 mo after Tx plus calcium 1000 mg/d and vitamin D 800 IU/d	calcium 1000 mg/d and vitamin D 800 IU/d	*BMD:* stable (+1%, =NS) at LS in PAM group vs. decline (−6%). Stable at FN and TH in both groups. *Fractures:* NS between groups
Coco 2012 [103]	42 (20/22)	12	RIS 35 mg/w plus calcitriol 0.25 μg/d	Placebo plus calcitriol 0.25 μg/d	*BMD:* stable at LS and TH in both groups. *Fractures:* 2 vertebral in RIS group. *Biopsies:* maintenance of bone volume, mineralized volume, trabecular thickness, no evidence of adynamic bone disease
Smerud 2012 [78]	123(65/58)	12	IBN i.v. 3 mg every 3 mo plus calcitriol 0.25 μg/d and calcium carbonate 1000 mg/d	i.v. placebo every 3 mo plus calcitriol 0.25 μg/d and calcium carbonate 1000 mg/d	*BMD:* similar with IBN vs. placebo at LS (+1.5 vs. +0.5%), increase at TH (+1.3 vs. −0.5%) and radius (+0.6 vs. −1.9%). *Fractures:* 1 vertebral in IBN and 1 in placebo group
Sanchez-Escuredo 2015 [224]	69 (35/34)	12	IBN per os 150 mg/mo *OR* RIS 35 mg/w	–	*BMD:* equally increased with both PAM and ALN at LS and FN. *Fractures:* NR
Bonani 2016 [82]	90 (46/44)	12	Dmab every 6 mo plus calcium 1000 mg/d and vitamin D 800 IU/d	Calcium 1000 mg/d and vitamin D 800 IU/d	*BMD:* increased at 12mo at LS, TH and FN in Dmab compared to placebo (+5.1%, +1.9% and +1,1%, respectively). *Fractures:* no fractures. *Other:* increased volumetric BMD and cortical thickness at the distal tibia and radius in HR-pQCT. More common hypocalcemia and urinary tract infections with Dmab. No effect on graft rejection
Marques 2019 [70]	32 (16/16)	12	ZOL i.v. 5 mg at the time of Tx plus cholecalciferol 50,000 UI/mo	Cholecalciferol 50,000 UI/mo	*BMD:* increased more with ZOL than in controls at LS (+5.6 vs. +1.1%) and FN (+5.8 vs. +2.5%). *Fractures:* no fractures. *HR-pQCT:* ZOL partially prevented trabecular bone loss at tibia but not at radius with no changes in porosity in either site. *Biopsies:* post-Tx worsening of trabecular connectivity and improvement in cortical thickness and porosity with no difference between groups

Abbreviations: ALN, Alendronate; BMD, Bone Mineral Density; CLO, Clodronate; Dmab, denosumab; ETI, etidronate; FN, femoral neck; qod, every other day; IBN, ibandronate; iv, intravenous; LS, Lumbar Spine; NR, not reported; NS, non-significant; PTH, parathyroid hormone; PAM, pamidronate; RIS, risedronate; mo, month; Rx, treatment; TH, Total hip; TPTD, teriparatide; Tx, transplantation; w, week; ZOL, zoledronic acid.

0.053 g/cm2 and 0.055 g/cm2 (unweighted gain of 7.4% and 6.0%), respectively, compared with controls, with no effect on fracture incidence but also no adverse effects on graft function or calcium levels [108]. Similarly, Kan et al. who analyzed 17 RCTs (1067 patients) with BPs administration, reported a BMD increase at the LS and FN of 0.05 g/cm2 and 0.03 g/cm2 (5.5% and 5.0%), respectively, and no effect on fracture rates [109]. Similarly, Versele et al., by analyzing 19 RCTs and quasi-RCTs (959 patients), found a 6.0% and 5.6% change in BMD at LS and FN, respectively, at 12 months [110]. Finally, in a recent network meta-analysis, Yang et al. included 21 RCTs (1332 patients) with BPs in KTRs [111]. All BPs (alendronate, pamidronate, risedronate, ibandronate, zoledronic acid) except for clodronate significantly increased LS BMD while only pamidronate and ibandronate achieved significant gains at FN BMD. The combination of calcium and vitamin D analogs was significantly less effective than either pamidronate or alendronate. Similarly to the other meta-analyses, no effect on fracture risk was found. Low fracture event incidences, small sample sizes, and short follow-up duration in all these studies and meta-analyses probably limit the ability to draw conclusions regarding fracture risk. In an earlier meta-analysis (9 studies, 625 patients), evaluating fracture risk not only in KTRs but in solid organ transplant recipients in general, one-year BP treatment reduced the overall number of fractures, but not specifically vertebral fractures [83].

Besides the questionable efficacy of antiosteoporotic agents in KTRs, safety concerns are also raised. BPs should be administered with caution due to their potential nephrotoxicity and the risk of deterioration of adynamic bone disease [112]. Furthermore, a decrease of serum calcium and a risk for worsening secondary hyperparathyroidism with BP administration has been reported [113]; however, most studies reported no difference in serum calcium or PTH levels between BP-treated patients and controls [114,115]. Increased incidence of transient, usually asymptomatic, hypocalcemia has also been documented with denosumab [82]. Additionally, at least BPs, may be associated with the occurrence of atypical femur fractures (AFF) and osteonecrosis of the jaw (ONJ) in this patient population. It should also be remembered that these patients frequently have other risk factors associated with medication-related osteonecrosis of the jaw (MRONJ) development [116]. There are few reports of AFF. Nonetheless, consideration should be given to the risk of MRONJ and AFFs in such patients. No adverse effect of BPs [76,78,113] or denosumab [82] on graft function has been reported.

Low vitamin D concentrations are among the factors associated with osteo/sarcopenia in KTRs [117]. The transplanted kidney begins to synthesize calcitriol, often within hours of transplantation, and this affects parathyroid activity, reducing PTH concentrations substantially but not enough to reach normal levels, so even KTRs with optimal outcomes in terms of renal function do not achieve full suppression of PTH. Treatment with active vitamin D could result in suppression of PTH. Indeed, treatment with alfacalcidol or calcitriol ameliorates bone loss during the first months post-transplantation [74,78] and probably has a beneficial effect on the preservation of bone mass in the long-term in KTRs, that may be similar or even higher than alendronate [112]. However, the usefulness of calcium and vitamin D is limited in KTRs with persistent hyperparathyroidism and hypercalcemia. A large RCT (NCT01431430) [118] evaluating the 2-year effect of high (100,000 IU) versus low (12,000 IU) monthly vitamin D3 administration in KTRs with vitamin D levels < 30 ng/ml has been completed but results are pending.

Besides GCs, which adversely affect BMD and fracture risk as mentioned above, proton pump inhibitors (PPIs), which are widely prescribed for KTRs, were associated with increased hip fracture risk in a large case-control study [119]. Additionally, poor vitamin K status was associated with low BMD and increased fracture risk in KTRs [120]. Whether vitamin K supplementation will be beneficial for bone health in this setting is currently unknown.

The 2017 KDIGO CKD-MBD guidelines [47] recommend BMD testing in KTRs if the results will impact treatment decisions. According to these guidelines, in the first 12 months after kidney transplant with an eGFR > 30 ml/min/1.73 m2 and low BMD, treatment with vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents should be considered. After the first 12 months data are insufficient data to guide treatment. A bone biopsy could be considered prior to antiresorptive or other osteoporosis therapies to assist selection of the most appropriate treatment depending on the type of bone disease.

4.2. Liver transplantation

4.2.1. Bone disease in hepatic insufficiency

Bone disease in patients with end-stage liver disease, characterized by both low bone mass or decreased mineralization (osteomalacia), is called hepatic osteodystrophy. It is common, with rates below the osteoporotic cut-off (BMD) accounting for 20–40% of patients awaiting orthotopic liver transplantation (OLT) [121–123]. Importantly, morphometric vertebral fractures have been reported in about 25–30% of these patients [123,124]. Apart from common factors adversely affecting bone metabolism (age, BMI, smoking, alcohol use, low calcium intake, vitamin D deficiency, concomitant diseases and medications), cirrhosis itself (especially primary biliary cirrhosis) and related morbidity (e.g. hypogonadism, low IGF-1 levels, malnutrition, and sarcopenia) further aggravate bone disease [125]. The severity of bone disease before OLT is regarded as predictive of bone loss and fracture risk after OLT [125,126].

Among patients awaiting OLT, 65–90% have low 25OHD concentrations [123,127–129], with 13% having levels < 2.5 ng/ml [129]. This may be partly due to impaired hepatic 25-hydroxylation of cholecalciferol in hepatic failure. Nonetheless, PTH and calcium levels (especially albumin-corrected calcium, given the low albumin levels in hepatic failure) remain largely within their respective normal ranges, and secondary hyperparathyroidism is not common [128]. Vitamin D-binding protein is also decreased in hepatic failure, resulting in low-normal free 25OHD levels [129], which may deter the development of secondary hyperparathyroidism. Histomorphometric studies indicate that patients with hepatic osteodystrophy have abnormally low bone matrix mineralization combined with decreased cortical bone volume, low bone formation and slightly elevated bone resorption parameters, which all can contribute to increased fracture risk [130]. More recently, hepatic osteodystrophy has been associated with reduced numbers of osteoprogenitor cells and ineffective bone repair mechanisms [131].

4.2.2. Evaluating fracture risk

Since bone disease [121–123], including vertebral fractures [123,124], is common in patients with hepatic failure, it is recommended that patients awaiting OLT undergo DXA to evaluate LS and hip BMD, and spine radiographs or VFA to identify possible vertebral fractures. Despite the high prevalence of bone disease and low-energy fractures before and early after OLT, hepatic failure and liver transplantation have not yet been incorporated as a cause of secondary osteoporosis into FRAX or other tools used to calculate fracture risk. Therefore the use of these tools may underestimate fracture risk in patients with hepatic failure and/or subjected to OLT, even if GC use is included in most tools.

Based on existing data on natural history of the disease after OLT [126,132], spine radiographs or VFA may be repeated 3–6 months after OLT to diagnose possible new vertebral fractures. DXA testing is advised to be repeated at the two years after OLT, because of the lower rates of bone mass restoration at the hip, although differences at LS BMD could be observed sooner (e.g. within one year). Since longer-term data are scarce, subsequent follow-up should be individualized.

4.2.3. Post–transplant bone disease

OLT is associated with accelerated bone loss within the first 3–6 months at the LS and the FN [125,126], which results in new low-

Table 2
Controlled clinical trials using active treatment regimens for the prevention of bone loss associated with liver transplantation.

Reference	Patients (active/control)	Duration (mo)	Active regimen	Control regimen	Findings summary
Valero 1995 [140]	40 (40/77)	12	Calcitonin im 40 U/d or ETI 400 mg/d, 15 d/3 mo plus calcium 945 mg/d	No intervention	*BMD:* LS increased similarly in calcitonin (6.4%) and etidronate group (8.2%) at 12 mo, whereas decreased (−3.4%) in CON group; FN data NR. *Fractures:* NR
Neuhaus 1999 [134]	484 (238/246)	18	Calcitriol (0.25 or 0.5 μg/d) with or without calcium 1000 mg/d, and with or without sodium fluoride 25 mg/d	No intervention	*BMD:* LS and FN increased in calcitriol compared with CON group at 18 mo; better results were observed with the combination of calcitriol, calcium and fluoride (10.7% in LS and 12.8% in FN). *Fractures:* lower rates of clinical fractures in calcitriol [2 (0.8%)] than CON group [7 (2.8%)] at 18 mo.
Ninkovic 2002 [144]	99 (45/54)	12	PAM iv 60 mg, a single before transplantation	No intervention	*BMD:* LS remained unchanged in both groups; FN similarly decreased in PAM (4.3%) and CON group (3.5%) at 3 mo and remained stable up to 12 mo. *Fractures:* morphometric vertebral fractures in 3 (6.7%) in PAM and 1 (1.9%) in CON group (NS); non-vertebral fractures in 1 (2.2%) in PAM and 1 (1.9%) in CON group (NS).
Hommann 2002 [148]	36 (17/19)	12	IBN iv 2 mg/3 mo plus calcium 1000 mg/d and vitamin D 800–1000 U/d	Calcium 1000 mg/d and vitamin D 800–1000 U/d	*BMD:* LS increased in IBN (about 2%), whereas decreased in CON group (about −1.5%) at 12 mo; FN decreased in both groups initially and returned at baseline values in IBN (about +1%), but not in CON group (about −4.5%) at 12 mo. *Fractures:* NR.
Dodidou 2003 [145]	79 (21/58)	24	PAM iv 30 mg/3 mo plus calcium 1000 mg/d and vitamin D 800–1000 U/d	Calcium 1000 mg/d and vitamin D 800–1000 U/d	*BMD:* LS increased more in PAM group at 12 (8.6%) and 24 mo (10.4%) than CON group (0.3% and 1.8%, respectively); FN increased in PAM at 12 (3.2%) and 24 mo (7.0%), whereas decreased in CON group (−1.6% and 1.1%, respectively). *Fractures:* clinical fractures in 2 (6.3%) in ZOL and 0 (0%) in CON group (NS).
Millonig 2005 [141]	136 (98/38)	48	ALN (dosage NR) plus calcium 1000 mg/d and vitamin D 400 U/d	Calcium 1000 mg/d and vitamin D 400 U/d	*BMD:* LS increased in ALN at 24 mo and remained stable thereafter, whereas remained stable in CON group; FN increased in ALN at 12 mo and remained stable thereafter, whereas remained stable in CON group. *Fractures:* Overall 5.8%; comparative data between groups NR.
Crawford 2006 [150]	62 (32/30)	12	ZOL iv 4 mg/3 mo plus calcium 600 mg/d and ergocalciferol 1000 U/d	Placebo plus calcium 600 mg/d and ergocalciferol 1000 U/d	*BMD:* LS increased in ZOL (about 3% at 6 mo and 4% at 12 mo), whereas decreased in CON group at 3 mo (about −3.5%) and progressively increased up to 12 mo (about 2.5%); FN remained stable in ZOL, whereas decreased in CON group (about −4% at 3 mo and −3% at 12 mo). *Fractures:* clinical fractures in 2 (6.3%) in ZOL and 2 (6.7%) in CON (NS).
Atamaz 2006 [142]	98 (49/49)	24	ALN 70 mg/w plus calcium 1000 mg/d and calcitriol 0.5 μg/d	Calcium 1000 mg/d and calcitriol 0.5 μg/d	*BMD:* LS increased more in ALN group at 12 (5.1%) and 24 mo (8.9%) than CON group (0.4% and 1.4%, respectively); FN increased in ALN at 12 (4.3%) and 24 mo (8.7%), whereas in CON group decreased at 12 mo (−1.1%) and returned to baseline at 24 mo (0.6%). *Fractures:* vertebral fractures in 3 (6.8%) in ALN and 7 (14.6%) in CON (NS); non-vertebral in 0 (0%) in ALN and 2 (4.2%) in CON group (NS).
Pennisi 2007 [146]	85 (43/42)	12	PAM iv 30 mg/3 mo plus calcium 1000 mg/d and vitamin D 800–1000 U/d	Calcium 1000 mg/d and vitamin D 800–1000 U/d	*BMD:* LS remained similarly unchanged in PAM (−0.1%) and CON group (−0.6%); FN similarly decreased in PAM (−4.7%) and CON group (−5.9%). *Fractures:* clinical fractures in 1 (2.3%) in PAM and 3 (7.1%) in CON group (NS).
Monegal 2009 [147]	79 (38/41)	12	PAM iv 90 mg at baseline and 3mo plus calcium 1000 mg/d and vitamin D 16,000 U/15d	Placebo plus calcium 1000 mg/d and vitamin D 16,000 U/15d	*BMD:* LS increased in PAM group (2.9%), but not in CON group (1%); FN similarly decreased in both groups (about −3%). *Fractures:* vertebral in 7 (18.4%) in PAM and 3 (7.3%) in CON group (NS).
Bodingbauer 2010 [151]	96 (47/49)	12 (treatment) 24 (follow-up)	ZOL iv 4 mg, 8 infusions during 12 mo plus calcium 1000 mg/d and vitamin D 800 U/d	Calcium 1000 mg/d and vitamin D 800 U/d	*BMD:* LS data NR; FN similarly increased in both groups at 12 mo. *Fractures:* lower rates of clinical fractures in ZOL [4 (8.5%)] than CON group [11 (22.5%)] at 24 mo.

(*continued on next page*)

Table 2 (*continued*)

Reference	Patients (active/control)	Duration (mo)	Active regimen	Control regimen	Findings summary
Kaemmerer 2010 [149]	74 (34/4)	12 (treatment) 24 (follow-up)	IBN 2 mg/3mo plus calcium 1000 mg/d and vitamin D 800–1000 U/d	Calcium 1000 mg/d and vitamin D 800–1000 U/d	*BMD*: After initial decrease in both groups, LS returned to baseline in IBN (−0.2%), whereas decreased in CON group (−3.2%) at 12 mo; FN decrease decreased in IBN (−2.2%) and CON group (−4.1%) at 12 mo. *Fractures*: lower rates of clinical fractures in IBN [2 (7.4%)] than CON group [8 (25.8%)] at 24 mo.
Guadalix 2011 [143]	89 (45/44)	12	RIS 35 mg/w plus calcium 1000 mg/d and vitamin D 800 U/d	Calcium 1000 mg/d and vitamin D 800 U/d	*BMD*: LS increased in both groups (1.5% difference between groups favoring RIS, but NS); FN remained stable in both groups. *Fractures*: vertebral in 4 (10%) in RIS and 8 (21%) in CON group (NS).
Shane 2012 [152]	41 (31/10)	12	ZOL iv 5 mg/y or ALN 70 mg/w plus calcium 945 mg/d and vitamin D 1000 U/d	Placebo plus calcium 945 mg/d and vitamin D 1000 U/d	*BMD*: LS increased similarly in ZOL (2.7%) and ALN (3.2%), while decreased in CON group (−2.6%); FN remained stable in ZOL and ALN, while decreased in CON group (−3.3%). *Fractures*: NR specifically for liver transplantation patients.

Abbreviations: ALN, Alendronate; BMD, Bone Mineral Density; CON, control; ETI, etidronate; FN, femoral neck; IBN, ibandronate; im, intramuscular; iv, intravenous; LS, Lumbar Spine; NR, not reported; NS, non-significant; PAM, pamidronate; RIS, risedronate; mo, month; w, week; ZOL, zoledronic acid.

energy fractures in 20–35% of patients during this period, mainly at sites where trabecular bone predominates (vertebrae and ribs) with vertebral fractures being the most prevalent [122,124,126,127,132,133]. Patients with pre-transplant osteoporosis, the elderly [126] and individuals with previous vertebral fracture(s) [122] are at higher risk of fractures post-transplant. Furthermore, LS BMD loss is associated with higher GC doses, and is more prominent in patients treated with cyclosporin (−5–6%) than tacrolimus (−3–4%) at 6 months, which is possibly due to higher GC doses used in cyclosporin-treated patients [33,134]. Although FN BMD decreases similarly at 6 months in patients treated with cyclosporin and tacrolimus (−5%) [134], higher bone loss at FN has been observed at 2 years when comparing cyclosporin (−5%) to tacrolimus treatment (−1.5%) [33].

Six months after OLT, a progressive improvement in bone mass starts, initially at the LS (trabecular bone), in accordance with BMD and histomorphometric evidence of increased bone formation [126], which reaches pre-transplantation values at two years post-operatively. FN BMD also progressively improves, but remains lower than respective pre-transplantation values 3–5 years post-transplantation [126,132]. Factors favoring LS bone gain are successful transplantation with normal hepatic function and improved gonadal status, premenopausal status (in women), lower cumulative GC dose, lack of cholestasis and higher vitamin D and PTH levels [125].

Bone turnover increases after OLT [135]. Both P1NP and CTX increase by 50–60% six months after OLT compared to their pre-transplantation levels [135], indicative of an enhanced osteoblastic and osteoclastic activity, respectively. Both RANKL and OPG increase within days of OLT, thus contributing to the up-regulation of bone turnover [136]. PTH concentrations are also higher one month post-OLT, but this increase appears to be transient, with baseline levels being restored 3 months after OLT [127]. These changes may be related to initially high GC doses that are tapered over time, cyclosporin A or tacrolimus administration, as well as to the gradual improvement of liver and gonadal function after OLT.

4.2.4. *Preventing and managing bone disease post-transplantation*

A cornerstone for limiting bone disease after OLT is the minimization of GC use; GC tapering and withdrawal accelerates the recovery of bone mass in patients following a successful OLT [137]. Existing evidence does not favor the use of tacrolimus over cyclosporine [33,134].

Although conclusive data explicitly for patients subjected to OLT are lacking, achievement and maintenance of normal calcium and vitamin D levels is recommended, as is the case for patients with GIOP [138]. Elemental calcium intake is recommended at a dose of 1000–1200 mg/day. Dietary intake of calcium should be encouraged and supplementation should be given to those who cannot meet the optimal dietary intake. In this regard, the calculation of dietary intake can be based on a calcium calculator launched by the International Osteoporosis Foundation (https://www.iofbonehealth.org/calcium-calculator). Regarding vitamin D, given its very low levels in some patients [129], special care should be taken to restore 25OHD concentrations at levels regarded as optimal (> 30 ng/ml) in patients with GIOP. Due to impaired hepatic 25-hydroxylation of cholecalciferol, at least before OLT, higher than usual doses of cholecalciferol may be needed to restore 25OHD levels. To date, low rates of vitamin D and calcium supplementation have been reported, being lower than 10% of patients in some studies [139].

There is also no consensus on the use of antiresorptive and osteoanabolic medication in patients before and/or after OLT. Generally, there is lack of sufficiently powered RCTs with hard endpoints (e.g., low-energy fractures). There are also scarce head-to-head comparative studies to favor one agent over the others. It remains largely inconclusive to whom and when (before or after OLT) treatment should start. Last but not least, there are many cofounders in different studies (e.g., multiple comorbidity, different immunosuppressive agents, different GC doses), which further limit the generalization of their results. For all

these reasons, the management of bone disease associated with OLT remains largely empirical and should be individualized.

The effects of different agents on BMD and fracture prevention in patients with bone disease associated with OLT are summarized in Table 2. Calcitonin [140] and calcitriol [134] have been used in older studies, while oral (etidronate [140], alendronate [141,142], risedronate [143]) and intravenous BPs (pamidronate [144–147], ibandronate [148,149], zoledronic acid [150–152]) have been used in most recent ones. Generally, a favorable effect has been shown in most, but not all, studies regarding BMD, which is more striking at the LS than the FN. A meta-analysis has also confirmed a favorable effect of BPs at LS, but not FN BMD [153]. Based on the aforementioned natural history of bone disease after OLT [126,132], probably longer-term trials are required to show a favorable effect on FN. Owing to the lack of head-to-head comparative studies, we cannot recommend one BP over the others; alendronate or risedronate may be selected from the oral formulations, whereas zoledronic acid could be selected for patients with gastroesophageal AEs, given its potency and simpler dosage scheme compared with other intravenous BPs.

Since GCs are administered to all patients subjected to OLT and fractures may occur even at patients with normal BMD, treatment might be considered for all transplant recipients. However, a more moderate approach would be the administration of BPs in patients with moderate-to-high risk of fracture, based on the guidelines for GIOP [138]. The optimal time to start BPs seems to be early after OLT. The use of BPs before OLT has been also proposed as a preventive measure, but pamidronate administration before OLT was not sufficient to limit bone loss after OLT [144]. It is highlighted that 25OHD levels should be restored before the use of antiresorptive treatment; otherwise, the osteomalacia of hepatic osteodystrophy may be deteriorated. Furthermore, BPs should be used with caution in patients with low bone turnover before OLT, although adynamic bone disease is not as prominent in patients with liver failure, as in patients with renal failure.

Although, denosumab could be an alternative antiresorptive treatment, as is the case in patients with GIOP [138], it has not been adequately studied in patients after OLT. In an uncontrolled small study, denosumab showed favorable effects on BMD in patients after OLT [154]. Therefore, denosumab may be currently suggested for patients undergoing OLT with concomitant renal failure, in whom BPs are contraindicated. Hormonal replacement therapy could be also considered in women with concomitant ovarian failure, but evidence is limited only to older studies without BMD or fracture data [155]. To the best of our knowledge, other agents including raloxifene, and osteoanabolic medications such as teriparatide and abaloparatide, have not been studied in patients with OLT.

4.3. Heart transplantation

4.3.1. Bone disease in cardiac insufficiency

Patients with congestive heart disease awaiting heart transplantation frequently present with low bone mass. Shane et al. reported osteoporosis in 19% and osteopenia in 42% of 101 patients with severe congestive heart failure referred for cardiac transplant evaluation [156], while other studies have validated lower BMD in patients suffering from congestive heart failure as compared to age- and gender-matched controls [157,158]. Although the etiology of low BMD in congestive heart failure is not fully understood, factors associated with cardiac insufficiency that may contribute to bone loss comprise reduced exercise or immobilization, sarcopenia, lack of sunlight exposure, low calcium intake, use of loop diuretics leading to urinary calcium loss, heparin administration, smoking and excessive alcohol intake, as well as other common osteoporosis factors [156,159,160]. Furthermore, severe right heart insufficiency accompanied by congestive liver disease may result in reduced hepatic synthesis of 25OHD, while kidney impairment resulting from congestive heart failure itself or the use of diuretic or vasodilating drugs may affect $1,25(OH)_2D$ synthesis. Indeed vitamin D deficiency and secondary hyperparathyroidism have been reported in patients with severe congestive heart failure [156]. Magnesium depletion, which may result from the use of diuretic therapy, is another putative contributor to osteoporosis in this setting [161]. An additional risk factor is hypogonadism caused by the debilitating heart disease [160,162].

4.3.2. Evaluating fracture risk

Since bone disease is common in patients with congestive heart failure and outcome of transplantation might be influenced by spine and rib fractures, all patients awaiting transplantation should receive a comprehensive evaluation including fracture history, a routine bone densitometry of the LS and FN measured by DXA and spine radiographs or VFA to diagnose prevalent fractures [81,159]. In one study, vertebral compression fractures (anterior wedge or total body) were detected in 14% of patients with congestive heart failure awaiting heart transplantation [157]. A longitudinal monocentric study using multivariate analysis reported that pre-transplant BMD at the LS or hip as well a history of fracture were significant risk factors for the development of osteopenia or osteoporosis after cardiac transplantation [163]. Another multivariate analysis study identified age and LS BMD before transplantation as the only predictors of fracture [133].

4.3.3. Post–transplant bone disease

Significant bone loss after heart transplantation is common and contributes to an increased risk of fracture-related morbidity and mortality. The most rapid rate of bone loss occurs within the first year, with BMD decreases ranging from 3 to 10% at the LS and 6 to 11% at the FN [156,163–168], which is probably induced by the high doses of GCs administered immediately after transplantation [169]. After the first post-operative year there is attenuation in bone loss or even a partial BMD recovery [163,165,166].

The initial post-transplantation period is characterized by an increase of bone resorption markers and a concomitant decrease of bone formation markers, mostly reflecting the effects of GCs on bone metabolism [169]. In general bone formation markers normalize by 6 to 12 months after cardiac transplantation [167]. The transient impairment in bone formation has an even more significant impact in pediatric cardiac transplant recipients (CTRs) since it can hamper the acquisition of peak bone mass. A histomorphometry study in children revealed low trabecular bone volume (32% of patients) and low bone turnover in 32% of CTRs, primarily due to decreased bone formation [170]. Data on bone biopsies of adult CTRs are scarce, with one study failing to identify correlations between histomorphometric findings and biochemical changes [171].

Notwithstanding the consensus of clinical studies on the natural history and pattern of bone loss, there is some controversy on the issue of the ability of BMD to fully reflect bone fragility after heart transplantation. A long-term follow-up study of a large cohort of CTRs revealed a discrepancy between DXA measurements (osteoporosis identified in 13% of LS and 25% of femur scans) and radiological evidence of vertebral fractures (40% of spine X-rays) [172]. Thus, standard densitometric criteria might be unreliable to identify bone fragility after cardiac transplantation, as is the case in the setting of GIOP [138,173] and type 2 diabetes. Furthermore, the FRAX tool commonly utilized in clinical practice to evaluate the 10-year probability of fracture might not accurately estimate fracture risk in CTRs, despite the fact that adjustments according to varying doses and duration of GCs use are available for FRAX [174].

Irrespectively of the ability of DXA and FRAX to fully predict fracture risk in this population, an increased prevalence of radiologically confirmed fragility fractures ranging from 14% to 40% has been reported [133,157,166,172,175–178].

4.3.4. Preventing and managing bone disease post-transplantation

Limiting factors of prevention studies in post-transplantation

Table 3
Randomized controlled trials using active treatment regimens for prevention of bone loss after heart transplantation.

Reference	Patients (active/control)	Duration (mo)	Active regimen	Control regimen	Findings summary
Braith 1996 [179]	8/8	6	Resistance training	No treatment	*BMD:* LS and FN bone loss was attenuated in the exercise group towards pre-transplant levels. Control group BMD loss 3%. *Fractures:* NR
Sambrook 2000 [186]	44/21[a]	24	Calcitriol 0.5–0.75 μg for 12 or 24 mo, calcium 600 mg/d	Placebo, calcium 600 mg/d	*BMD:* FN (but not LS) bone loss was attenuated in the calcitriol groups at 12 months. LS bone loss was similar among all 3 groups. *Fractures:* NR
Krieg 2001 [191]	11/17	36	PAM 60 mg every 3 months, calcium 1000 mg/d, vitamin D 1000 mg/d	Calcium 1000 mg/d, vitamin D 1000 mg/d	*BMD:* LS continuous increase over 3 years in the PAM group. FN loss over first year, complete recovery over 3 years in the PMN group. *Fractures:* NR
Braith 2003 [181]	16/9	6	ALN 10 mg/d or ALN 10 mg/d plus resistance training	No treatment	*BMD:* LS and FN increased significantly more in the ALN plus resistance training group vs. alendronate or control groups. *Fractures:* NR
Ippoliti 2003 [192]	32/32	12	CLO 1600 mg/d, calcium 2000 mg/d	Placebo, calcium 2000 mg/d	*BMD:* LS significant increase in CLO group, no difference in forearm. *Fractures:* 9.3% in placebo group vs 0% in CLO group.
Shane 2004 [187]	74/75	12	ALN 10 mg/d, calcium 945 mg/d, vitamin D 1000 IU/d	Calcitriol 0.5 μg/d, calcium 945 mg/d, vitamin D 1000 IU/d	*BMD:* Similar small losses at LS and TH in both groups. *Fractures:* no difference.
Braith 2006 [180]	10/8	6	Calcitonin 200 IU/d plus resistance training	Calcitonin 200 IU/d	*BMD:* Calcitonin alone did not rescue LS bone loss, but calcitonin plus exercise attenuated restored LS bone loss in pre-transplant levels. *Fractures:* NR
Fahrleitner-Pammer 2009 [193]	17/18	12	IBN 2 mg every 3 mo, calcium 500 mg/d, vitamin D 400 IU/d	Placebo, calcium 500 mg/d, vitamin D 400 IU/d	*BMD:* LS and FN remained unchanged in the IBN group but was reduced in the placebo group (−25% LS and −23% FN). *Fractures:* 13% in IBN group vs. 53% in placebo group.
Gilfraguas 2012 [194]	120/102	24	ALN 10 mg/d or ETI 400 mg/d or calcitonin 200 IU/d, calcium 1000 mg, vitamin D 800 IU/d	Calcium 1000 mg, vitamin D 800 IU/d	*BMD:* LS decreases in ETI, calcitonin and control group, and increased in ALN group (+5%) FN and TH decreased in all groups. *Fractures:* no difference.

Abbreviations: ALN, Alendronate; BMD, Bone Mineral Density; CLO, Clodronate; ETI, etidronate; FN, femoral neck; IBN, ibandronate; LS, Lumbar Spine; NR, not reported; PAM, pamidronate; mo, months; TH, Total hip.
[a] Study included 47 cardiac and 18 single lung transplants.

osteoporosis include small numbers of subjects, lack of randomization and absence of fracture data, thus preventing generalization of results. Three small prospective RCTs evaluated the efficacy of resistance exercise either alone [179], or in conjunction with either calcitonin [180] or alendronate [181], reporting an add-on effect of exercise in restoring BMD in CTRs. Although smoking and excessive alcohol consumption are known risk-factors for osteoporosis [182,183], there are no studies assessing the effects of interventional programs on bone health in the heart transplant populations to date. Furthermore, although low body mass index (BMI [kg/m^2] has been identified as an important osteoporosis risk factor [184], no systematic evaluation of the impact of BMI on osteoporosis development in this patient cohort has been performed to date.

There is limited and conflicting evidence to support therapeutic calcium supplements in prevention and treatment of bone loss after cardiac transplantation. Shane et al. reported that supplementation with elemental calcium (1000 mg/day) and vitamin D (400 IU/day) did not prevent significant bone loss after transplantation [166], while Meys et al. found that LS BMD was maintained in patients receiving 25 μg/d of calcidiol with calcium supplements [175]. In contrast, in another small prospective study in CTRs 1, 25 dihydroxy-cholecalciferol failed to reproduce this protective effect on spine bone mass [185]. Two more recent studies investigating the effect of calcitriol (0.5–0.75 μg/day) reported a reduction of bone loss either only at the femur [186], or at all skeletal sites [187].

Calcitonin is approved by the EMA as a short-term treatment for acute bone loss after immobilization, a second-line treatment of Paget's disease and cancer-induced hypercalcemia. The addition of calcitonin to calcium and vitamin D did not have a beneficial effect on BMD [185], and was found to be less effective when compared to etidronate or calcidiol [188]. In addition, one investigation concluded that calcitonin prevented early LS BMD loss after cardiac transplantation but was unable to restore BMD in a period of up to 7 years [189].

A series of clinical studies have investigated the use of BPs to prevent increased bone resorption and rapid bone loss following cardiac transplantation. An initial report on the use of etidronate was discouraging since it found higher rates of bone loss in comparison to calcium and vitamin D supplementation [190]. Studies with second- and third-generation formulations have yielded more promising results. Krieg et al. reported that quarterly infusions of 60 mg of pamidronate started after cardiac transplantation and administered over 3 years led to a continuous increase in BMD at the LS, while BMD at the femur decreased in the first year but recovered totally after 3 years of treatment [191]. Alendronate (10 mg/d) significantly reduced bone loss at all skeletal sites compared to placebo, and this effect was comparable to that observed with calcitriol (0.5 μg/day) [187]. One year of oral clodronate therapy (1600 mg/day in two divided doses) also resulted in a significant increase in BMD at the LS of 64 CTRs [192]. A more recent study of intravenous ibandronate in male CTRs reported a reduction of fractures and preservation of bone mass with favorable effects on bone turnover also being supported by histomorphometric findings [193]. In a study comparing the effects of calcitonin, etidronate, and alendronate in preventing bone loss during the first 2 years after heart transplantation, only alendronate therapy was associated with a significant increase in BMD at the LS and femur [194]. A recent meta-analysis on the efficacy of BPs concluded that when administered in the early stage after cardiac transplantation, BPs effectively reduced the loss of bone mass, especially at the LS [195]. Studies on risk of fracture with BPs are lacking.

There are no studies on the effects of denosumab, teriparatide, or selective receptor modulators (SERMs) on bone health post cardiac-transplantation to date. The impact of hormone replacement therapy after cardiac transplantation has not been thoroughly investigated, although an older study in hypogonadal men had reported that testosterone supplementation started 6 month post-operatively and administered in conjunction with calcium and vitamin D stabilized LS BMD within 24 months [196]. Table 3 provides an overview of RCTs using active treatment regimens for prevention of bone loss after cardiac transplantation.

4.4. Lung transplantation

4.4.1. Bone disease in respiratory insufficiency

Patients with end-stage respiratory disease awaiting lung transplantation commonly have osteopenia or osteoporosis [197–202]. Many of these patients have significant risk factors for osteoporosis, such as older age, postmenopausal status, smoking, decreased ambulation, loss of body weight and muscle mass, chronic obstructive pulmonary disease (COPD), and GC use [159,197]. Whether the effects of inhaled GCs differ from those of oral and intravenous GCs is not known. Their systemic absorption is estimated to be around 10–20%, thus inhaled GCs could result in potentially similar effects as oral GCs. Studies that have compared the effects of inhaled versus oral GCs have come to varying conclusions, while comparisons between the two therapies may be affected by the overlap between groups [203]. Although patients with COPD are primarily at a high risk of osteoporosis due to GC treatment, histomorphometric studies have confirmed that low bone mass and microarchitecture deterioration also characterize COPD patients who are not on GCs [204]. With regard to the pathophysiology of pre-transplant bone disease, patients with cystic fibrosis (CF) constitute a distinct category of lung transplant recipients. Patients with CF commonly present with additional risk factors of impaired bone health such as hypogonadism [205], an inflammatory cytokine milieu which induces bone resorption [206], and pancreatic insufficiency causing malabsorption [207]. As a consequence also osteomalacia can be a manifestation of bone disease in patients with CF awaiting lung transplantation [208].

4.4.2. Evaluating fracture risk

As mentioned above, the high prevalence of osteoporosis in patients with end-stage respiratory disease supports the pre-transplant assessment with routine bone densitometry of the LS and hip measured by DXA [81,159] and a detailed history of fractures. Furthermore, spine radiographs or VFA should be performed since there is radiological evidence of vertebral fractures in up to 30% of patients awaiting lung transplantation [197,200,202].

4.4.3. Post–transplant bone disease

Rates of bone loss at the LS and femur range from 2 to 5% in the first year after lung transplantation [200,209]. Furthermore, fracture rates are also increased, with prospective studies reporting ranges from 15% to 37% [209,210]. Histomorphometric data derived from postmortem vertebral bone biopsy samples of 11 lung recipients with CF denote severe osteopenia in trabecular and cortical bone, with decreased osteoblast and increased osteoclast activities [211]. Regarding the status of 25OHD, Aris et al. reported a gradual increase from the low concentrations seen before transplantation to normal levels, which is probably related to the use of vitamin D supplements [199].

4.4.4. Preventing and managing bone disease post-transplantation

Two small-scale RCTs have investigated the effects of resistance exercise on BMD changes after lung transplantation. Mitchell et al. reported that 6 months of resistance training led to a significant increase in LS BMD reaching pre-transplantation levels [212]. In a similar approach Braith et al. showed that the combination of resistance exercise and alendronate was more effective than alendronate alone in restoring bone loss [213].

A prospective observational study of 42 lung recipients reported that antiresorptive therapy (either intravenous pamidronate or hormone replacement therapy) but not calcium/vitamin D supplementation was able to restore LS BMD [214]. Another prospective non-randomized study showed that antiresorptive treatment with pamidronate

Table 4
Randomized controlled trials using active treatment regimens for prevention of bone loss after lung transplantation.

Reference	Patients (active/control)	Duration (mo)	Active regimen	Control regimen	Findings summary
Aris 2000 [216]	16/18	24	PAM 30 mg every 3 months, calcium 1000 mg/d, vitamin D 800 IU/d	Calcium 1000 mg/d, vitamin D 800 IU/d	*BMD:* LS and TH increased significantly more in the PAM group vs. controls. *Fractures:* NR
Sambrook 2000 [186]	44/21[a]	24	Calcitriol 0.5–0.75 μg for 12 or 24 mo, calcium 600 mg/d	Placebo, calcium 600 mg/d	*BMD:* FN (but not LS) bone loss was attenuated in the calcitriol groups at 12 months. LS bone loss was similar among all 3 groups. *Fractures:* NR
Mitchell 2003 [212]	8/8	6	Resistance training	No treatment	*BMD:* LS returned to pre-transplant levels in exercise group. Control group further lost BMD. *Fractures:* NR
Braith 2007 [213]	20/10	8	ALN 10 mg/d or ALN 10 mg/d plus resistance training	No treatment	*BMD:* LS increased significantly more in the ALN plus resistance training group vs. ALN or control groups. *Fractures:* NR

Abbreviations: ALN, Alendronate; BMD, Bone Mineral Density; LS, Lumbar Spine; NR, not reported; PAM, pamidronate; mo, months; TH, Total hip.
[a] Study included 47 cardiac and 18 single lung transplantation.

preserved or increased BMD before and after lung transplantation and resulted in only 4% of new fractures [215]. These results were reproduced in the setting of an RCT comparing the effects of pamidronate with calcium/vitamin D supplementation [216]. There are no studies on the effects of denosumab, teriparatide, or selective receptor modulators (SERMs) on bone health post lung-transplantation to date. There has been concern that denosumab may be associated with an increased risk of e.g., lung infections in post-lung transplant patients. There are no data on the safety of denosumab after lung transplantation, although a recent study in GIOP patients showed a similar safety profile for denosumab compared to risedronate and superiority in terms of LS and BMD increases [217]; furthermore, denosumab therapy was well-tolerated and improved bone density after liver, kidney and/or pancreas transplantation [154]. Table 4 provides an overview of RCTs using active treatment regimens for prevention of bone loss after lung transplantation.

5. Recommendations on prevention and treatment of transplantation-related osteoporosis

5.1. Pre-transplantation measures

Given existing ample data confirming the high prevalence of bone disease in patients awaiting solid organ transplantation, it is our expert opinion that all transplant candidates should be assessed for osteoporosis and fractures and, if indicated, treated before transplantation. The evaluation should include a fracture history, routine DXA testing of the LS and hip, spine radiographs or VFA, estimation of BTM under standardized conditions, and biochemical testing to identify secondary causes of osteoporosis. It is imperative to address lifestyle factors such as immobilization, smoking and alcohol abuse and critically assess current medications and minimize the use of those negatively affecting bone health. The FRAX tool, commonly utilized in clinical practice to evaluate the 10-year probability of fracture in primary and secondary osteoporosis, needs further evaluation to ascertain that it can accurately estimate fracture risk in organ transplant recipients, although adjustments according to varying doses and duration of GCs use have been introduced [174]. Although TBS correlates with bone microarchitecture and has been used to improve fracture risk prediction in the setting of renal transplantation, to our knowledge it has not yet been validated for other organ recipients. The use of HR-pQCT has yielded important information about effects of organ transplantation at individual bone compartments; however, lack of large-scale availability prevent its wide implementation at this time. Especially for KTRs, a bone biopsy pre-transplantation may help treatment decisions post-transplantation by identifying the specific type of the underlying bone disease, and thus the rate of bone turnover.

5.2. Post-transplantation measures

Since bone loss in the early post-transplanation period is uniformly observed in all solid organ recipients and is associated with GC administration, the goal should be to use the lowest possible doses and to taper and withdraw GCs as early as possible. Supplementation with calcium and vitamin D to maintain serum levels above 50 nmol/l seems reasonable. In KTRs where 1α-hydroxylation may be impaired, alfacalcidol or calcitriol may be indicated. Limited data on BPs and scarce data on denosumab have revealed some efficacy in terms of BMD improvement. Thus, these agents could be considered as treatment options in patients undergoing solid organ transplantation. There is not enough data to support the use of osteoanabolic agents, hormone replacement therapy or SERMs to date. Lacking solid evidence, it is even more important to apply the principal of individualized treatment in these patients.

6. Conclusions

Bone loss and increased fracture risk in the setting of organ transplantation are direct consequences of both the underlying disease, comorbidity and the immunosuppression regimens implemented after successful organ transplantation. Characteristics of bone disease may differ depending on the organ that fails and may need different diagnostic and therapeutic approaches.

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Appendix A. Supplementary data

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