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NEPHROLOGY - REVIEW

# Osteoporosis after renal transplantation

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**Abstract** Bone loss and fracture are serious sequelae of kidney transplantation, associated with morbidity, mortality and high economic costs. The pathogenesis of post-transplantation bone loss is multifactorial and complex. Pre-existing bone mineral disease is responsible for a significant part, but it is aggravated by risk factors emerging after renal transplantation with immunosuppressive agents being one of the key contributors. The decrease in bone mass is particularly prominent during the first 6–12 months after transplantation, continuing at a lower rate thereafter. Bone mineral density measurements do not predict bone histology and bone biopsy findings reveal heterogeneous lesions, which vary according to time after transplantation. Currently, vitamin D and bisphosphonates are the most extensively tested therapeutic agents against this accelerated bone loss in renal transplant recipients. Both of these agents have proven effective, but there is no evidence that they decrease fracture risk. More studies are needed to examine the complex pathophysiologic mechanisms implicated in this population, as well as the effects of different therapeutic interventions on bone disorders after kidney transplantation.

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## Introduction

Renal transplantation is a principal treatment option for end-stage kidney disease. As the number of renal transplant recipients (RTRs) along with their survival increase, a need for a better recognition of long-term complications of renal transplantation has ensued. Osteoporosis and fragility fractures constitute significant short- and long-term complications of renal transplantation that have been extensively studied. However, there are still issues regarding pathogenetic mechanisms, risk factors and treatment options that need to be further elucidated.

The decrease in bone mass is particularly prominent during the first 6–12 months after transplantation, continuing at a lower rate thereafter. The long-term prevalence of osteopenia and osteoporosis and associations with the risk of fractures are not well known. Existed literature report a 50 % prevalence of osteopenia and 15–56 % prevalence of osteoporosis during long-term follow-up of RTRs [1].

Although osteoporosis after solid organ or stem cell transplantation is a well-recognized entity [2], kidney transplantation associated osteoporosis is multifactorial and a rather complex condition. Bone mineral density (BMD) measurements do not predict bone histology and bone biopsy findings reveal heterogeneous lesions, which vary substantially according to early or later phases after transplantation. Moreover, in the setting of chronic kidney disease (CKD), it is difficult to differentiate osteoporosis from the spectrum of bone diseases associated with CKD. Yet this differentiation is significant for multiple reasons,

including the fact that management strategies differ vastly [3, 4].

## Pathogenesis and risk factors

Osteoporosis after kidney transplantation is multifactorial, while pathophysiologic mechanisms responsible for this condition are not completely elucidated [5].

Pre-transplantation risk factors include duration of dialysis, high or low parathormone (PTH) levels and pre-existing bone disease. Post-transplantation risk factors associated with bone loss and/or fractures are deceased kidney donor, immunosuppressive regimen choice (glucocorticoids, calcineurin inhibitors), time since transplantation, hypophosphatemia and graft dysfunction. Additional risk factors such as postmenopausal status for women and presence of diabetes have been considered as possible culprits, in adjunction to the classical osteoporosis risk factors such as age and female gender (Table 1). The final result of this multifactorial process which is determined by an increase in osteoclastic resorption and decrease in bone formation is an imbalance in bone turnover that leads to bone mass loss which persists long after transplantation.

Several clinical and experimental studies have attempted to identify specific risk factors associated with mineral bone disease and particularly osteoporosis after renal transplantation. There is no doubt that pre-transplantation renal osteodystrophy plays an important role in the maintenance or development of post-transplantation alterations of bone remodeling. Most RTRs have various forms of pre-existing bone disease that may persist after transplantation. Persistent secondary hyperparathyroidism, nonsuppressible nodular parathyroid hyperplasia and de novo secondary hyperparathyroidism that results from progressive functional alterations of the renal allograft might be responsible for at least some of the skeletal and mineral abnormalities following renal transplantation. However, in many studies, the bone histopathologic findings are heterogeneous, without apparent correlation with post-transplantation serum PTH levels, suggesting that other factors which become active after transplantation could play a central role in the development of these bone alterations [6–8]. An important role of PTH has been suggested in preserving osteoblast number and activity after transplantation by preventing apoptosis [9]. Nevertheless, it is worth mentioning that two studies which assessed bone biopsy samples in RTRs did not find a correlation between serum PTH levels and bone turnover [10, 11].

**Table 1** Risk factors for bone loss and fractures in RTRs

| |
|---|
| Female gender |
| Postmenopausal status in women |
| Increased age |
| Diabetes |
| Duration of dialysis prior to transplantation |
| High or low pre-transplantation PTH or presence of bone mineral disease |
| Deceased renal transplantation |
| Time since transplantation |
| Cumulative dose of glucocorticoids |
| Graft dysfunction |

Risk factors for osteoporosis were assessed in a clinical trial, enrolling 77 RTRs aged 17–50 years who had undergone renal transplantation 6 months to 2 years previously. Bone mineral densitometry was performed using dual-energy X-ray absorptiometry (DEXA). The incidence of osteoporosis was 26 %. The most common sites of osteoporosis were the hip and the spine. There was a significant relationship between post-transplantation creatinine concentration and hip osteoporosis. No relationship was observed between osteoporosis and age, sex, body mass index, duration of hemodialysis therapy before transplantation, cumulative dosage of any medications, or use of pulsed methylprednisolone therapy. A hip or spine *Z* score of 1 or less had no relationship to the number of steroid pulse sessions, but was significantly related to the total dosage of cyclosporine (CsA), prednisolone and mycophenolate mofetil (MMF) [12].

Another clinical study evaluated risk factors for osteoporosis after renal transplantation. Forty-four patients with end-stage CKD, who underwent kidney transplantation, were prospectively followed up for 12 months. All patients received prednisone with either CsA/MMF or tacrolimus/MMF therapy. Spine, hip, and whole-body BMD were measured at 12 months after transplantation. Results showed that 46 % of patients were normal, 43 % osteopenic and 11 % osteoporotic. Significant risk factors for osteoporosis were younger age and pre-transplant high intact PTH levels. Moreover, vitamin D receptor Bsm I polymorphism was found to be a predictor of bone loss [13].

A recent cross-sectional study evaluated 389 stable RTRs who underwent bone mineral densitometry assessment by DEXA at the lumbar spine, total hip and femoral neck. Independent associations with reduced BMD included female sex and lower body mass index for all sites, age for total hip and femoral neck, and hyperparathyroidism and time since transplant for the femoral neck. Interestingly, no association was found between renal function or 25-OH vitamin D level and reduced BMD at any site [14].

Opelz and Döhler analyzed data on hip fractures occurring in the first 5-year post-transplant among RTRs from deceased donors for transplantations performed between 1995 and 2008. In the population analyzed, the cumulative

rate of hip fracture during the first 5-year post-transplant was 0.85 %. Cox regression analysis identified the following risk factors, female recipients aged 40–59 years [hazard ratio (HR) 2.26, $p = 0.029$], female recipients 60 years or older (HR 5.14, $p < 0.001$), male recipients 60 years or older (HR 2.39, $p = 0.028$) and donor age ≥60 years (HR 1.75, $p = 0.009$). There was also a significant association between the number of HLA-DR mismatches and the diagnosis of osteoporosis during the follow-up period [15]. Another recent retrospective clinical trial evaluated 103 RTRs with a minimum of 12-month post-RT follow-up. The mean glomerular filtration rate (GFR) of osteoporotic patients was significantly lower and PTH levels significantly higher [16].

Glucocorticoid-induced suppression of bone formation is probably the most important factor in the genesis of early and long-term bone loss. Steroids are directly toxic to osteoblasts and lead to increased osteoclast activity. They also have other effects that promote calcium loss and development of osteopenia. These include decreased calcium absorption in the gut, reduced gonadal hormone production, diminished insulin-like growth factor-1 production, decreased sensitivity to PTH, increased activity of receptor activator of nuclear factor kappa beta ligand (RANKL) and increased osteoclastogenesis [17, 18]. Subsequently, as suggested by Cunningham, the effects of age, gender, PTH and CsA on bone volume and bone turnover of RTRs have been consistently overridden by the prominent effects of glucocorticoids [19, 20].

Data regarding other immunosuppressive drugs in post-transplant renal osteopathy and osteoporosis are still controversial, as elegantly summarized in a recent review [21]. In particular, in vivo animal studies have shown that CsA causes bone loss which is associated with increased bone formation and resorption [22], while other studies have resulted in completely different findings suggesting that CsA induces in vivo inhibition of resorption and stimulation of formation in rat bone [23].

From the clinical relevant studies, an earlier report has indicated that bone mass loss was not different for the CsA monotherapy, azathioprine and prednisolone dual therapy, or triple immunosuppressive therapy groups [24]. Another study comparing DEXA and bone biopsy findings in 13 patients receiving CsA monotherapy versus 12 patients receiving azathioprine and prednisolone dual therapy showed no significant differences in BMD between the groups. Both prednisolone and CsA were associated with slight osteoclast stimulation and osteoblast suppression and marked retardation of mineral apposition and bone formation rates. Both drugs were also associated with reduced BMD at the axial and appendicular skeleton, even though a nonsignificant trend toward a better-preserved lumbar spine BMD was observed in the CsA group [25].

The second calcineurin inhibitor, tacrolimus, also causes trabecular bone loss in animals, but data regarding skeletal effects in humans are limited. A prospective study, involving 86 RTRs, 65 on tacrolimus-based immunosuppression and 21 on CsA-based immunosuppression, was conducted to investigate the long-term evolution of BMD. BMD measurements in lumbar spine and femoral neck were performed by DEXA in the first month after transplantation (baseline) and yearly thereafter up to the fourth year. One-third of patients had bone loss mainly during the first year of follow-up that was associated with higher baseline BMD, high steroid dose and lower calcitriol levels at 1 year, whereas late administration of calcitriol and calcium supplements did not improve post-transplant osteopenia. More than 50 % of total patients were osteopenic 4 years after transplantation [26].

A more recent study evaluating the impact of calcineurin inhibitors on bone metabolism in RTRs enrolled 66 patients with good graft function (GFR values >60 mL/min) and intact PTH levels <100 pg/mL, with a 4-year follow-up. Calcineurin inhibitors caused mild osteoblastic proliferation and matrix mineralization activity, as reflected by increased osteocalcin and alkaline phosphatase levels. This bone formation activity, however, was counterbalanced as depicted by a threefold increase in urine deoxypyridinoline levels which correlated with BMD scores. Thus, the study suggested that calcineurin inhibitor-based immunosuppression with low maintenance doses of glucocorticoids induces slight bone formation but relatively potent, clinically relevant bone resorption [27].

Although MMF, sirolimus and azathioprine do not affect bone volume in animal studies [28–30], an in vitro study suggested that sirolimus might interfere with the proliferation and differentiation of osteoblasts [31]. There are scarce data in humans regarding everolimus, which seems to reduce cancellous bone loss in ovarectomized rats by decreasing osteoclast-mediated bone resorption [32].

## Evolution of post-transplantation osteoporosis

Bone mass loss after kidney transplantation leading to osteopenia or osteoporosis is reported to occur primarily in the first 12 months, affecting mainly the cortical bone. The most rapid decline in BMD, measured by DEXA, occurs in the first 6 months after transplantation and seems to decelerate thereafter, a fact which has been attributed to the minimization or elimination of corticosteroids. Accordingly, past reports have shown that BMD decreases significantly at a mean of 5.5–19.5 % during the first 6 months after transplantation [5, 6, 33] but only 2.6–8.2 % between months 6 and 12 [34] and 0.4–4.5 % thereafter [35, 36].

Changes of bone mass late after transplantation have been more controversial. Carlini et al. [7] reported that BMD in a group of long-term RTRs progressively improved with time after transplantation, approaching normal values after 10 years. Nevertheless, data from a retrospective analysis of lumbar BMD from RTRs between 6 and 20 years after renal transplantation showed a mean annual decrease in lumbar *T* scores of $-0.6 \pm 1.9$ %, a value that is relatively similar to the observed decline in the general population with aging. The mean annual BMD loss was statistically indistinguishable between men and women, but low estradiol levels were associated with accelerated bone loss in postmenopausal women [37]. Another study evaluating the incidence of osteopenia and osteoporosis versus vertebral fractures in RTRs with stable graft function and with a follow-up of at least 10 years revealed that osteopenia and osteoporosis were common among long-term RTRs (25 and 50 % prevalence of lumbar spine osteoporosis and osteopenia, respectively) and both were associated with poorer graft function [38].

A very recent study regarding long-term changes in BMD in RTRs evaluated a total of 326 patients who underwent 766 DEXA during an average of 8.2-year follow-up. At baseline (first scan; median 0.5 years after transplantation), bone density was slightly below average for age and sex. At the second scan (mean 2.7 years after first scan), mean bone density *Z* scores have increased. The only factor associated with a significant BMD change at all sites was osteoporosis treatment (BMD increase). Even after restricting the analysis to recipients who had not received osteoporosis treatment, final mean bone density was average for age and sex suggesting that with routine BMD monitoring and management, post-transplant bone density typically remains stable or improves with mean values that are average for age and sex [39].

## Diagnostic evaluation

In RTRs, a noninvasive cost-effective tool regarding diagnostic evaluation of osteoporosis is BMD monitoring with DEXA scans, although there are a number of limitations. Results of the DEXA scans are interpreted according to the World Health Organization (WHO) classification of osteoporosis, but it is important to note that WHO definition of osteoporosis and relevant classification are unlikely to be applicable in CKD patients and in RTRs [4]. This fact is supported by the poor correlation between BMD and fracture risk, and the limited information BMD provides with regard to bone quality or turnover in RTRs [5]. Thus, the indication for DEXA scanning after renal transplantation is unclear. Nevertheless, both Kidney Disease Outcomes Quality Initiative (K/DOQI) and Kidney Disease Improving Global Outcomes (KDIGO) have published guidelines concerning the evaluation of bone disease RTRs by using DEXA scans [40, 41].

According to K/DOQI, DEXA scans should be obtained at time of transplant and at first and second 2 years post-transplant. If the BMD *T* score is $\leq -2$ at the time of the transplant or at subsequent evaluations, consideration should be given to therapy with bisphosphonates if not contraindicated [40].

KDIGO guidelines suggest that, among RTRs with GFR $\geq$ 30 mL/min/1.73 $m^2$, BMD should be measured in the first 3 months post-transplant if the patients are receiving corticosteroids and/or if there are risk factors for osteoporosis. On the other hand, they suggest that BMD testing not be routine in patients with stage 4–5 CKD (GFR < 30 mL/min/1.73 $m^2$), since it does not predict the type of bone disease or fracture risk [41]. A bone biopsy should also be considered, particularly prior to bisphosphonate therapy.

With regard to alternative noninvasive diagnostic tools in the complex entity of osteoporosis in RTRs, trabecular bone score (TBS) could be considered as an option. TBS is a gray-level textural metric that can be extracted from the two-dimensional lumbar spine DXA image. TBS is related to bone microarchitecture and provides skeletal information that is not captured from the standard BMD measurement [42]. Existing data derived from different patients' populations, but not yet from RTRs suggest that TBS is a possible valuable future clinical tool in the diagnosis of osteoporosis and in fracture risk assessment in kidney transplantation.

According to bone biopsy, which remains the gold standard for the diagnosis of post-transplantation mineral bone disease, most patients after transplantation had adynamic bone disease [43]. Rojas et al. [9] showed that osteoid volume, osteoid thickness, osteoid resorption surface and osteoclast surface were above the normal range before transplant and remained so approximately 35 days after transplantation; however, osteoid and osteoblast surfaces significantly decreased within 35 days after transplant and there was also inhibition of bone formation and mineralization as well as apoptosis, which correlated with the dose of administered glucocorticoids. In contrast to the above findings, a longitudinal study of 57 patients [44] reported more heterogeneous biopsy findings. Thus, mild osteitis fibrosa and osteitis fibrosa, the most frequent forms of renal osteodystrophy, were observed in 22.8 and 24.6 % of the patients, respectively, mixed uremic osteodystrophy was found in 12.3 %, adynamic renal bone disease was found in 5.3 %, and osteomalacia was found in 3.5 %. Moreover, 13 patients (22.8 %) displayed reduced bone mass and structural damage without typical signs of renal osteodystrophy. Only five patients (8.7 %) showed normal histomorphometric parameters. In conclusion, the main alteration in

**Table 2** Potential therapeutic approaches of bone loss in RTRs

| Therapeutic approach | Effect on BMD |
|---|---|
| Glucocorticoid minimization/ withdrawal | Decrease loss |
| Vitamin D and vitamin D analogs | Decrease loss |
| Bisphosphonates | Decrease loss (possible net increase) |
| Calcitonin | Decrease loss (limited data) |
| Calcimimetics | Decrease loss (limited data) |
| Teriparatide | Decrease loss (limited data) |
| Denosumab | No data in RTRs |
| Exercise | No data in RTRs |
| Hormone replacement therapy | No data in RTRs |

bone remodeling after renal transplantation is a decrease in bone formation and mineralization, simultaneously with persistent bone resorption, which may lead to a remodeling disequilibrium in favor of resorption. Similarly, the defective bone formation may be a consequence of alterations in osteoblast function, decreased osteoblastogenesis or increased rates of osteoblast apoptosis.

More bone biopsies in RTRs are needed to better clarify the combined impact of pre-transplantation bone disease and immunosuppressive regimens on bone histology in this patient population. In this setting, it would be appropriate to perform bone biopsy in patients with symptoms of bone pain or muscular weakness without relevant laboratory findings, those with fragility fractures, or severe osteoporosis with low normal PTH, where diagnosis of osteomalacia should be ruled out before initiation of antiresorptive therapy.

## Post-transplantation fractures

Several publications have confirmed the increased fracture risk after renal transplantation as compared to chronic dialysis patients. Previous reports have shown that the overall fracture risk after renal transplantation is nearly four times higher compared to healthy individuals and is 30 % higher during the first 3 years after transplantation than in patients on dialysis [8, 45]. It is important to note that RTRs are at particular risk for vertebral fractures and that this risk is greater than their risk for lower extremity fractures [45].

A recent review of cohort studies that provided estimates on incidence and risk factors for fracture in RTRs including 262,678 recipients showed that fracture sites varied by study with a highly variable incidence rate ranging from 3.3 to 99.6 fractures per 1,000 person-years and the 5-year cumulative incidence for fracture varied ranging from 0.85 to 27 % [46]. However, a recent analysis regarding evaluation of secular trends in the incidence and outcomes of hip fractures in RTRs demonstrated that since 1997, case-mix-adjusted post-transplant hip fracture rates have declined substantially. Changes in immunosuppressive therapy appear to be at least partly, responsible for these findings [47].

Another interesting aspect is the relationship between BMD and fracture risk in transplanted patients. Although a low BMD is a potent fracture risk factor, previous studies have suggested that many RTRs with low BMD do not experience fractures [48]. Furthermore, a study by Duriex et al. [49] showed that 44 % of patients at least 5 years after transplantation had a history of fracture and more than one-third of these fractures occurred in patients with no BMD criteria of osteoporosis according to the World Health Organization. Similarly, Marcén et al. [38] showed that mild vertebral fractures were not associated with osteopenia or osteoporosis, as they occurred in a significant proportion of patients with normal BMD; still, lumbar spine osteoporosis was significantly associated with peripheral fractures.

However, these findings were challenged in a study which aimed to investigate whether DEXA is of value in predicting fractures by evaluating 238 RTRs, who underwent 670 DEXA between 1995 and 2007 [50]. The presence of osteopenia (46.0 %), osteoporosis (13.9 %) as well as absolute BMD (median 0.9) in the hip region was used to evaluate fracture risk. In all, 46 patients had 53 fractures. The authors showed significantly increased fracture risk for osteoporosis (3.5 times, CI 1.8–6.4, $p = 0.0001$) as well as for osteopenia (2.7 times, 1.6–4.6, $p = 0.0003$).

## Treatment

The management of bone disease after renal transplantation should taken into account treatment issues of renal osteodystrophy before renal transplantation, maintain focus on the prevention of bone disease during the first year, when the bone loss is most significant and finally the long-term treatment of decreased bone mass in the RTR (Table 2). In this context, it should be highlighted that post-transplantation bone disease is a complex disorder that extends beyond simple osteoporosis and includes systemic and local derangements of the bone and mineral metabolism that should be detected and treated accordingly. Thus, in the consideration for the management of osteoporosis, excluding renal adynamic bone disease, which is characterized by low osteoblastic activity and low bone formation rates, is very important [3]. Administering pharmacological agents approved for the treatment of osteoporosis, whose mechanism of action is to lower bone turnover when no bone turnover is evident, would be deleterious.

Published studies that have addressed these issues often have significant limitations that include lack of randomization, small sample size and treatment with different immunosuppressive agents or other drugs that potentially affect bone and mineral metabolism. Nevertheless, a previous review of 23 randomized controlled trials regarding interventions for bone disease after renal transplantation, including 1,209 patients revealed that although the trials were inadequately powered to show a reduction in the risk for fractures, bisphosphonates and vitamin D administration had a beneficial effect on BMD at the lumbar spine and femoral neck [51]. Additionally, the incidence of reported bisphosphonate toxicity was low.

The rationale for minimizing corticosteroid exposure is compelling and based on well-established risks of osteoporosis, avascular necrosis and other side effects. Even though some studies found beneficial effects of early tapering of prednisolone on BMD [52, 53], steroid withdrawal, when carried out weeks to months after kidney transplantation, may be associated with an increased risk of acute rejection. Data from a recent study evaluating the effects of early corticosteroid withdrawal (ECSW) protocols after kidney transplantation on fracture risk and bone quality were controversial [54]. The study results demonstrated that ECSW was associated with preservation of BMD at the central skeleton. On the other hand, it was associated with progressive declines in cortical and trabecular bone density at the peripheral skeleton.

Bisphosphonates have been shown to have beneficial effects in the treatment of postmenopausal osteoporosis. They act by inhibiting osteoclast-mediated bone resorption. Second- and third-generation bisphosphonates are very effective in preventing bone loss after transplantation.

In four studies of multiple doses of pamidronate during the initial months after renal transplantation, the prevention of bone loss occurred even after treatment was discontinued [55–58]. Most, if not all, studies suggest that pamidronate administration prevents bone loss shortly after transplantation, although low turnover bone disease may develop or worsen in many patients [55, 56]. Similar results were found when alendronate was administered [57–61]. A clinical trial comparing oral alendronate and intravenous pamidronate in 40 patients during the first 6 months after renal transplantation demonstrated that pamidronate was comparable to alendronate in preventing early bone loss, with more gastrointestinal side effects present in the alendronate group [62]. Intravenous ibandronate was used by Grotz et al. [63] in a randomized trial of 80 RTRs at a dose of 1 mg immediately before the transplant and 2 mg at 3, 6 and 9 months after transplantation and demonstrated the prevention of bone loss, spinal deformation and body height loss during the first year after transplantation. A recent randomized trial of intravenous ibandronate in 129 RTRs with early stable renal function, during the first 12 months after transplantation, showed that ibandronate significantly improved BMD in total femur and ultradistal radius and also suppressed biomarkers of bone turnover. It should be emphasized that all patients received calcium and calcitriol supplementation, which alone showed a very good efficacy and safety profile, virtually maintaining a stable BMD over 12 months after transplantation [64]. Another randomized controlled trial of 20 kidney transplant recipients showed that zoledronate improved the calcium content of cancellous bone [65]. In another study, zoledronate therapy conferred no sustained benefit versus placebo at 3 years after transplantation implicating that this early short-term intervention may not exhibit a sustained bone sparing effect in the long term [66]. Weekly oral risedronate immediately after renal transplantation can improve BMD, particularly in the femoral neck, 6 months after transplantation, without important side effects [67].

A meta-analysis of randomized controlled trials evaluating effects of bisphosphonates on bone loss in the first year after renal transplantation which included five studies involving 180 participants demonstrated that treatment with bisphosphonates had a substantial effect in preventing post-transplant osteodystrophy. Thus, BMD decline at the lumbar spine within 6–12 months after transplantation was significantly reduced by 0.06 g/cm$^2$ in patients treated with bisphosphonates, while at the femoral neck, the loss of BMD was reduced by 0.05 g/cm$^2$ during this period, but not with statistical significance. No major side effects were reported [68].

In order to evaluate the role of bisphosphonates and BMD measurements for the follow-up and management of bone loss and fractures in long-term RTRs, 554 patients were retrospectively studied. Results demonstrated that although bisphosphonates may prevent bone loss in long-term recipients, their role in preventing fractures is limited when they are initiated relatively late, after the first year of transplantation [69].

Since the amount of bone loss after transplantation does not necessarily predict fracture risk and its arrest or reversal has not been shown to parallel a decline in the rate of fractures, further studies that are based on a better categorization of patients with regard to histologic alterations should be conducted. Thus, there are no current solid recommendations regarding administration of bisphosphonates in the long term, following renal transplantation.

Vitamin D metabolites may have a potential role in preventing loss of bone mass after transplantation, mediated particularly by its effects on enhancement of calcium absorption, reducing PTH secretion as well as mitigating the bone-wasting consequences of glucocorticoids. A well-controlled, blinded study by Josephson et al. [70] showed that RTRs who were given calcium and calcitriol had significantly less bone loss in the lumbar spine and

increased BMD in the distal radius and femoral neck compared with patients given calcium alone or placebo. The treated patients did not develop significant hypercalcemia or deterioration of kidney function during the 2 years of the study. Torres et al. [71] reported that therapy with low-dose calcium supplements during 1 year, plus intermittent calcitriol for 3 months after transplantation, was well tolerated, suppressed PTH levels more rapidly and prevented bone loss at the proximal femur. Compared to placebo, treatment with calcidiol and oral calcium has resulted in increased BMD at the lumbar spine and femoral neck [72, 73].

Paricalcitol, a selective vitamin D receptor activator, also known as D mimetic is indicated in the prevention and treatment of secondary hyperparathyroidism; however, no study until now has assessed the association between bone fracture, BMD or outcomes and administration of paricalcitol.

Two recent clinical trials, including 64 and 182 RTRs, respectively, have assessed efficacy of combination therapy with bisphosphonates and vitamin D. Both trials demonstrated that combination therapy was the most effective regimen to improve BMD among RTRs, leading to significantly improved BMD measurements [74, 75].

In the past several years, the calcimimetic agent cinacalcet has been frequently evaluated for the treatment of hypercalcemia in RTRs with ongoing refractory hyperparathyroidism. A favorable effect of cinacalcet on BMD in the patients with persistent hyperparathyroidism was reported by several small studies [76–78]. Regarding calcitonin, preliminary data from a single-center study suggested that calcitonin may help to restore bone mass in RTRs with osteoporosis [79].

Another therapeutic agent studied in patients after kidney transplantation is teriparatide, a recombinant human PTH. Teriparatide has been compared with bisphosphonates in patients with osteoporosis who had received glucocrticoids with better results regarding improvements in BMD in the teriparatide arm [80]. A recent trial showed that teriparatide administered to RTRs for 6 months was well tolerated but did not change BMD in the lumbar spine or distal radius compared with the placebo group. However, BMD at the femoral neck remained stable in those given teriparatide compared with a decrease in the placebo group. In addition, after 6 months, no significant differences between the two groups were detected in fractures, bone histology, vitamin D levels, PTH levels, kidney function or serologic bone markers [81]. Teriparatide can be considered as an alternative treatment of mineral bone disease in RTRs with low PTH and refractory hypocalcemia [82].

Denosumab, a RANK-ligand inhibitor for the treatment of postmenopausal osteoporosis [83] can theoretically reduce osteoclastic resorption of trabecular structures and, therefore, be used for the treatment of osteonecrosis; but currently, there are no available human data.

Exercise training and hormonal therapy are other potential interventions in RTRs. The effect of regular exercise or hormone replacement therapy on bone loss or risk of fracture has not yet been examined in this population, although data from other solid-organ transplant patients are promising [84–86].

## Conclusion

Loss of bone mass following kidney transplantation is common. In the setting of pre-existing osteodystrophy, transplantation-specific therapies and reduced renal function because of a chronic failing allograft, new specific risk factors such as HLA-DR mismatch or VDR polymorphisms are emerging as well. Currently, there are no well-established therapeutic approaches; however, vitamin D analogs and bisphosphonates are often used for the treatment of osteoporosis after kidney transplantation. More studies are needed to examine the complex pathophysiologic mechanisms implicated, as well as the effects of different therapeutic interventions on bone disorders after kidney transplantation.

**Conflict of interest** All authors declare that they do not have any conflict of interest.

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