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REVIEW

Bone disease after kidney transplantation

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Summary

Post-transplant renal osteopathy (ROP) remains a serious problem, which contributes to substantial long-term morbidity of the graft recipients. Bone loss is most pronounced during the first months after engraftment; concerning bone density development in long-term transplant recipients, controversial data exist. The clinical impact of ROP is a marked increase in fracture rate following kidney transplantation compared with both general population and patients on dialysis treatment. The following review will focus on post-transplant ROP and discuss its epidemiology, the clinical features, factors contributing to the pathogenesis of this complication, as well as the evaluation, prevention and treatment options available for kidney allograft recipients.

Introduction

Organ transplantation has become a fairly common and effective modality for the treatment of several types of end-stage organ failure. Advances in immunosuppressive agents and transplant techniques during the last decades have led to improved long-term graft and patient survival. While successful transplantation is capable of reversing many complications of end stage organ failure, disturbances of bone and mineral metabolism persist contributing to substantial long-term morbidity of the recipients. Particularly during the early post-transplant period, graft recipients experience a rapid loss of bone mass. Consequently, the risk for fractures is clearly increased in this population. Osteoporosis is prevalent in more than half of solid organ recipients and vertebral fractures are found in almost a third of patients [1].

In daily medical routine, however, mainly the function of the engrafted organ is in the centre of our attention, especially in the early post-transplant period. Important comorbidities such as post-transplant osteopathy often stay in the background. Thus, although bone disease has been recognized as a common complication, the routine application of adequate diagnostic tools as well as treatment to prevent further bone loss is still often insufficient.

Pre-existing bone disease

Almost all patients undergoing kidney transplantation suffer from pre-existing bone disorders caused by chronic renal insufficiency and concomitant diseases. Consequently, post-transplant renal osteopathy (ROP) cannot be considered as a separate entity; rather its course is significantly conditioned by changes in bone structure and mineral metabolism existent before engraftment. There are several types of renal bone disease, based on histomorphometric features, with many patients showing evidence of more than one defined disorder [2]. Osteitis fibrosa is a high turnover bone disease because of secondary hyperparathyroidism, which is characterized by enhanced numbers of osteoclasts and osteoblasts leading to increased bone resorption. Osteomalacia shows low rates of bone turnover in combination with a mineralization defect and

accumulation of unmineralized osteoid. Elements of both, high and low bone turnover may be observed in mixed types of ROP. The adynamic bone disease is characterized by decreased bone remodeling activity, which may result from excessive suppression of the parathyroid glands or skeletal resistance to parathyroid hormone (PTH). The latter, which already develops during chronic kidney failure and could persist after transplantation, has been suggested to result from down regulation of PTH receptors in bone, inhibition of PTH binding to receptors by accumulation of 7–84 PTH fragments, or from decreased blood levels of bone morphogenetic protein-7 [3]. Adynamic bone disease is distinguishable from osteomalacia by a thin osteoid layer (Fig. 1).

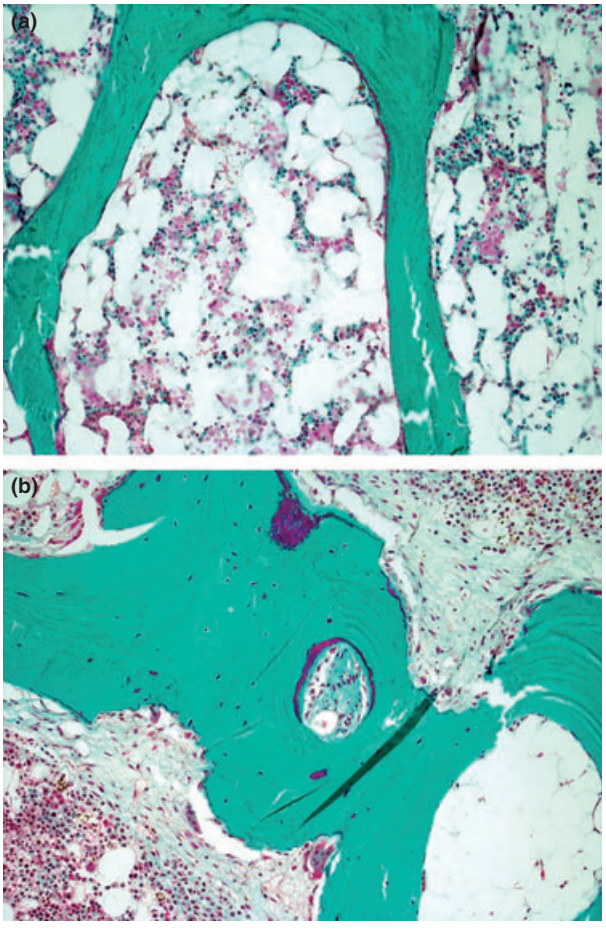

Figure 1 (a) Low turnover bone disease (adynamic bone disease): an extremely thin red osteoid rim can be seen on the bone surface of the green mineralized bone trabeculae without any bone cells. (b) High turnover bone disease: on the top and bottom of the green bone lamelle are multinucleated osteoclasts (arrow) absorbing the mineralized bone and there are collagen fibers in the bone lacunae. Other areas of the trabeculae are covered with red osteoid (Goldner staining, print magnification 500×); Courtesy of Irene Sulzbacher, MD, Osteopathology, Medical University of Vienna.

Epidemiology of bone disease after renal transplantation

Bone density loss remains a serious problem after renal transplantation and is most pronounced during the first months after engraftment. A large number of trials confirmed this early accelerated bone loss, and Kodras and Haas summarized their results concerning bone mineral density (BMD) development in a recently published review. In brief, almost all studies published since 1990 noticed a BMD loss at lumbar spine, if no bone sparing medication was used. In the first 6 months, bone loss ranged between 0.05% and 14.5% (median 4.1%) and persisted in the majority of cases at 1 year after engraftment, although at a lower level (range 0.1–8.2%; median 3.4%). At the femoral neck, bone loss was slightly less after 6 months but showed a tendency to increase further thereafter. Kodras and Haas summarized a BMD decline of 0.01–7.9% after 6 months (median 2.8%) and 0.8–9% (median 3.8%) after 12 months.

Controversial data exist concerning BMD development in long-term renal transplant recipients. Brandenburg *et al.* [5] showed that lumbar spine BMD was stable during a 2- year observation period, starting 47 months after engraftment. These results were confirmed in a subsequent study, which demonstrated no further significant bone loss after the first post-transplant year [6]. At all times however, BMD levels were significantly lower compared with those of healthy controls. Pichette *et al.* performed longitudinal BMD evaluations in 55 long-term renal graft recipients with a mean post-transplant time of 8.1 years and a follow-up period of 22 ± 5 months. In contrast to the above described findings, the authors noticed an ongoing reduction in lumbar spine BMD of 1.7% per year. This accelerated bone loss was significantly associated with higher prednisone dosage; and the relatively high steroid dosage used was discussed as a possible explanation for the discrepant results compared to Brandenburg's studies [7]. Grotz *et al.* [8], on the other hand, found BMD stabilization beyond the second post-transplant year, followed by an improvement of 1–2% per year thereafter.

The clinical impact of ROP and bone loss is a marked increase in the fracture rate following kidney transplantation from 0.012 fractures per patient and year on hemodialysis to 0.032 after engraftment [9]. Compared to healthy controls, the rise in fracture incidence varies between fivefold among male kidney recipients, 18-fold among female recipients aged 25–44 years and 34-fold among women aged 45–64 years [10]. Symptomatic bone fractures are more frequently located in the limbs compared with the axial skeleton, as shown in a large investigation of 432 renal graft recipients with 33 patients

suffering from 28 appendicular and five axial fractures [10]. In a cross-sectional study, Nisbeth *et al.* [11] noticed an osteoporotic fracture prevalence of 17% in renal graft recipients, and the majority of fractures occurred within the first three post-transplant years. A higher rate of 40% was found among recipients with diabetes type 1, compared to 11% in the nondiabetes group. Female gender was also associated with an elevated fracture rate of 23% in this study.

In contrast to the general population, however, low bone density has not been uniformly confirmed as a major risk predictor for fractures in renal transplant patients. Durieux *et al.*, who investigated the frequency and predictors of osteoporotic fractures in late kidney graft recipients (mean interval since transplantation 8.5 years), found a high rate of osteoporosis (53% of patients) and osteopenia (40% of patients), as well as fractures (44% of patients) in their study population. However, no statistically significant association between the occurrence of vertebral fractures and low BMD evaluated by DEXA was noticed. [12]. In accordance, Grotz *et al.* [9] found BMD measurements by DEXA of only limited value to define transplanted patients at increased risk for fractures as in the general population in elderly women [13]. The low correlation between fractures and bone mass was attributed to differences in the bone architecture, which were observed between renal allograft recipients and matched subjects with similarly reduced BMD values [14]. Thus, the altered three-dimensional trabecular bone architecture accounts for the higher fracture rate in transplanted patients and the fact that fractures may also occur despite normal BMD evaluations.

Causes of bone disease after renal transplantation

Glucocorticoids

The reasons for augmented bone loss, most pronounced during the first months after engraftment, are manifold, but corticosteroid therapy has been shown to be a major contributor, considering the fact that steroid doses used for maintenance immuno-suppression and to treat acute rejections are the highest during this period [15]. The etiology of glucocorticoid induced bone disorder is multifactorial [16–18]. Bone formation is profoundly inhibited by decreased replication and differentiation of osteoblasts with increased apoptosis of mature cells, as well as enhanced osteoclast activity. Other steroid effects that promote calcium loss and the development of bone disease include decreased intestinal calcium absorption, renal calcium wasting, and impaired gonadal hormone production, which in turn also reduces osteoblast activity. In addition to the direct effects on bone, steroids may induce a profound myopathy with muscle weakness, which additionally delays post-transplant mobilization with subsequent aggravation of bone loss.

The impact of steroids on bone density has been shown in several studies of renal transplant recipients. In a prospective trial, Aroldi *et al.* [19] found an increase in lumbar spine BMD in patients with cyclosporine monotherapy, whereas graft recipients with additional steroid treatment exhibited a sustained bone loss in the first 18 months after transplantation. Nowacka-Cieciura *et al.* [20] prospectively investigated the effect of steroid withdrawal at month 3 after engraftment and noticed a significantly increased BMD at all investigated sites, in contrast to ongoing prednisolone therapy with virtually unchanged BMD values during 2 years of observation. These results were confirmed by van den Ham *et al.* [21] with significant BMD decrease in steroid treated recipients compared to early withdrawal, especially at the lumbar region. The beneficial effect of steroid-free immunosuppression has also been shown in the forearm, with BMD loss during 5 years follow-up of 5% and 25%, respectively, in cyclosporine versus azathioprine plus prednisolone treated subjects [22].

Calcineurin inhibitors

There is no doubt that cyclosporine is not neutral in terms of bone metabolism, as *in vivo* animal studies showed long ago that it induced high turnover osteopathy with loss of bone volume [23,24]. In contrast to *in vivo* experiments, cyclosporine *in vitro* was associated with an inhibition of bone resorption and a low turnover bone state [25]. Tacrolimus exhibits effects in the rat model that are similar to those of cyclosporine [26]; however, limited data are available concerning the clinical impact on bone. A small study in liver transplant recipients showed a more favorable long-term effect on bone mass with tacrolimus therapy compared with cyclosporine, possibly associated with the ability to use decreased amounts of corticosteroids with the tacrolimus based immunosuppression [27]. Goffin *et al.* [28] found a bone sparing effect of low-dose steroids with tacrolimus compared to normal-dose steroids plus cyclosporine in renal graft recipients, which was maintained even if compared with a subgroup with similar prednisolone dosage.

Hyperparathyroidism

Although serum PTH concentrations decrease progressively during the first months after transplantation, persistent hyperparathyroidism is a frequent finding in kidney graft recipients [29]. Only 23% of long-term recipients with serum creatinine below 2 mg/dl show PTH levels

within the normal range, while values greater than twice the upper normal limit are not uncommon with 27% of the evaluated patients [30]. The most important risk factors for ongoing hyperparathyroidism are the duration of dialysis treatment, the severity of secondary hyperparathyroidism prior to transplantation and the development of nodular and/or monoclonal hyperplasia of the parathyroid glands [31]. As the process of involution may take from a few months to several years, the persistently high serum PTH concentrations have been attributed to the relatively slow decrease in the hyperplastic parathyroid gland mass [32]. Additional factors that may contribute to elevated PTH levels are an incomplete normalization of kidney function [30], relative hypovitaminosis D [33] and decreased intestinal calcium absorption caused by corticosteroids.

Several studies related persistent hyperparathyroidism to increased bone turnover and decreased bone density after transplantation. Torres *et al.* [34] demonstrated that patients with PTH concentrations >250 pg/ml at the time of engraftment experienced a higher rate of vertebral bone loss in the following 3 months than those with lower levels. Similar results were found by Torregrosa *et al.* [35] within the first 6 post-transplant months and a PTH cut-off value of 240 pg/ml. Ongoing hyperparathyroidism (PTH > 150 ng/l) as a major cause of aggravated bone loss in stable renal transplant patients was noticed by Heaf *et al.* [36] after 3 years of follow-up. However, the association between persistent hyperparathyroidism and decreased bone density might be mainly prevalent in short-term renal transplant patients, as cross-sectional studies in long-term recipients have not demonstrated a correlation between the prevailing PTH levels and BMD or several bone histomorphometry parameters [37,38]. On the other hand, the harmful PTH effects on post-transplant ROP were not supported by all authors. Casez *et al.* [39] prospectively followed 33 recipients for 18 months after kidney transplantation and grouped them according to their PTH status (PTH cut off 109 pg/ml) 1 week after engraftment. Patients with high PTH levels showed a significantly higher BMD in the limbs and the whole body, as well a trend at hip and trunk, but no notable difference at the spine.

Other risk factors

Although the influence of sex hormones on bone density is well known in the general population, only limited information is available in transplant patients. Cueto-Manzano *et al.* investigated the effect of serum hormone levels on bone in long-term kidney graft recipients. While serum testosterone in men did not predict any of the densitometric or histomorphometric variables analyzed, oestradiol levels in women correlated significantly with histological parameters of bone structure and osteoblast function [40]. These findings were supported by Brandenburg *et al.* [41], who demonstrated a correlation between low oestradiol levels and the extent of annual BMD loss in postmenopausal female graft recipients.

As observed in the general population, reduced physical activity and malnutrition were linked with accelerated bone loss. Accordingly, the severity of post-transplant bone loss has been shown to correlate well with the duration of hospitalization in the first 3 months after engraftment [42].

Evaluation of bone disease after renal transplantation

To assess the presence or development of osteoporosis, the current Kidney Disease Outcomes Quality Initiative (K/DOQI) Guidelines for bone disease in renal transplant recipients recommend that patients should be monitored for changes in their bone mass on a regular basis after engraftment [43]. Thus, BMD measurements by DEXA scans should be obtained at the time of transplantation as well as 1 and 2 years thereafter. If osteoporosis is identified by changes in bone density (t-score ≤ -2 SD), the guidelines recommend considering a therapy as will be discussed here later.

In the general population, bone density measurement by DEXA represents a widely used method in the diagnosis of osteoporosis. As discussed above, however, low BMD has not been uniformly confirmed as a major risk predictor for the occurrence of fractures in renal transplant patients [9,12]. Besides mineralization, bone strength and fracture rate are strongly determined by the three-dimensional architecture of the bone matrix. This information, however, requires the histological evaluation of a bone biopsy and cannot be adequately estimated by noninvasive diagnostic tools. Consequently, bone histology remains the gold standard for the exact classification of ROP. These biopsies are ideally performed at the iliac crest using local anesthetics. The routine application of this invasive and sometimes painful procedure, however, is hardly established in clinical medicine. A possibility to still make a clear diagnosis of ROP could be the performance of a bone biopsy during the transplant procedure. Thereafter, noninvasive procedures such as densitometry and the determination of serological markers of bone metabolism have been suggested to be useful for the sequential follow-up [44]. Serological markers of bone resorption are osteoprotegerin, pyrodinoline, bone specific type 5b tartrate-resistance acid phosphatase, and procollagen type 1 cross-linked carboxy-terminale telopeptid. Bone formation markers include bone-specific alkaline

phosphatase, osteocalcin, bone morphogenetic protein-7, procollagen type I carboxy-terminal extension protein, and N-terminal collagen type I propeptide. Other markers that are useful in ROP diagnostic but not produced by the bone itself are PTH, vitamin D3, aluminium and phosphatonins.

A substantial number of patients, however, develop low turnover bone disease during the post-transplant course, and neither PTH nor classical serologic bone markers reliably distinguish between the different forms of ROP [45]. Hence, to avoid further worsening of the underlying bone disease, a biopsy should be obtained before the initiation of a treatment, in particular, during the late post-transplant course.

Treatment options for bone disease after renal transplantation

Published treatment guidelines for bone disease in kidney graft recipients

Several guidelines were published to recommend treatment approaches for the prevention of bone disease aggravation as common complication following renal transplantation. The European Best Practice Guidelines 2002 advise the minimization of the administered cumulative glucocorticoid dose as well as an accompanying use of ergocalciferol or calcitriol with sufficient calcium intake during steroid treatment [46]. For patients with established osteopenia, bisphosphonate therapy should be considered, although the mode and duration of this treatment option are not discussed. Gonadal replacement therapy is recommended in patients where sex hormone insufficiency exists. Similarly, the K/DOQI guidelines 2003 suggest that the immunosuppressive regimen should be adjusted to the lowest effective dose of glucocorticoids [43]. If osteoporosis is identified by changes in BMD (t-score ≤ -2 SD), the guidelines recommend considering a therapy with parenteral bisphosphonates. Regarding Vitamin D or calcitonin treatment, no recommendations were published. No guidelines are available concerning the management of bone disease in kidney graft recipients from the Australian and Canadian Society of Nephrology or the British Transplantation Society.

Treatment options for post-transplant ROP

In view of the high prevalence of abnormal bone density and fractures in kidney graft recipients, several studies were carried out in the last years to evaluate the efficacy of anti-osteoporotic drugs. The number of randomized controlled trials in transplant patients, however, is limited and the magnitude of effect varies considerably across the studies. Therefore, tools such as meta-analysis can be applied to pool results, providing a more precise estimate of the effect.

For this reason, we recently analyzed the results of the available randomized controlled trials, which investigated the efficacy of bisphosphonate therapy in prevention and treatment of post-transplant ROP within the first year after successful engraftment [47]. This time frame was chosen because of the observation that bone loss is the highest in this early post-transplant period with subsequent slowing and in some cases even stabilization of bone density. Five studies involving 180 participants were included in this meta-analysis [48–52]. In order to reach optimal comparability of all studies, the authors were asked for the individual BMD results of all randomized patients, determined at lumbar spine and femoral neck at the time of engraftment as well as after bisphosphonate therapy. In brief, bisphosphonates showed a substantial effect in preventing post-transplant ROP. Compared to nontreated controls, BMD declined at the lumbar spine within 6–12 months after transplantation was significantly reduced by 0.06 g/cm^2 (95% CI 0.05–0.08 g/cm^2) (Fig. 2). At the femoral neck, the loss of BMD was reduced by 0.05 g/cm^2 (95% CI 0.0–0.11 g/cm^2) during this period (Fig. 3). This benefit could be reached without major side effects and without deterioration of kidney transplant function following bisphosphonate therapy, and none of the studies noted withdrawals because of serious adverse events. However, the individual trials were inadequately powered to assess the effect on fracture rate, which still remains the ultimate study end point for the evaluation of osteoprotective interventions.

Besides one small study, all investigators used intravenous infusions of bisphosphonates, which were applied two to four times, first at the time of transplantation, last one to nine months thereafter [48–51]. These regimens of two to four parenteral doses were simple to administer, obviously well tolerated and required minimal additional monitoring of the patients throughout the post-transplant period. Moreover, this way of application ensures high compliance and avoids the practical difficulties of oral bisphosphonates in these complex patients receiving multiple therapies. The optimal duration and dosage of this early bisphosphonate use, however, remain to be determined.

As shown by Coco *et al.* [48], prolonged and more intensive treatment may increase the risk of adynamic/low turnover bone disease. In this study, 72 new renal transplant recipients were randomly assigned to either pamidronate (at baseline and months 1, 2, 3 and 6) with vitamin D plus calcium or only vitamin D plus calcium, and bone biopsies were obtained at baseline and after 6 months in a subgroup of 14 subjects. The follow-up bone histomorphometry revealed adynamic bone disease

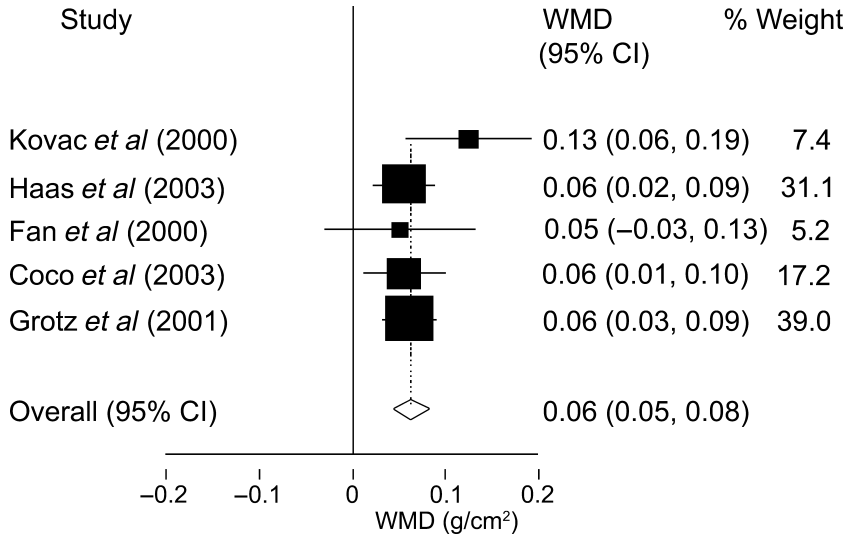

Figure 2 Weighted mean differences (WMD) and 95% confidence intervals (CI) of BMD change 6–12 months following transplantation at lumbar spine after bisphosphonate therapy versus control for individual studies (■) and the pooled results of all studies (◇); adapted from Mitterbauer *et al.* [47].

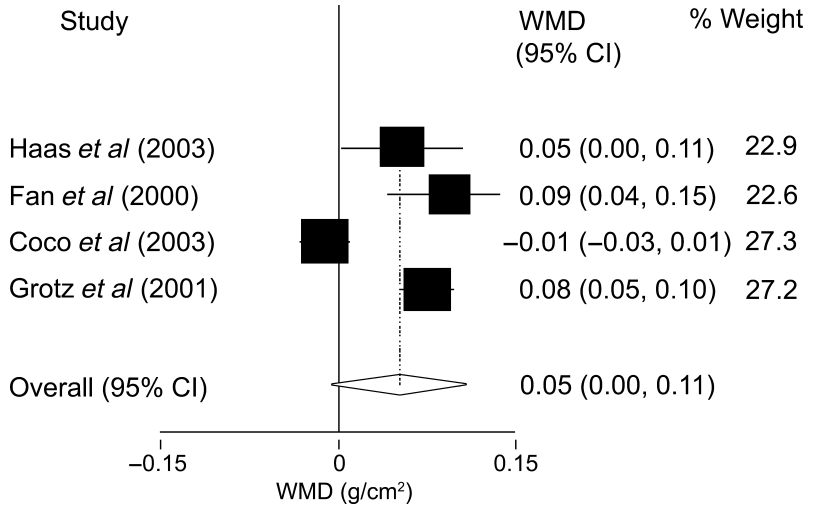

Figure 3 Weighted mean differences (WMD) and 95% confidence intervals (CI) of BMD change 6–12 months following transplantation at femoral neck after bisphosphonate treatment versus control for individual studies (■) and the pooled results of all studies (◇); adapted from Mitterbauer *et al.* [47].

in all pamidronate treated patients, five of six subjects newly developed adynamic bone disease and one continued to have it. In the control group, on the other hand, only 50% showed a decrease in bone turnover compared to baseline values. Whether an improved BMD in combination with low bone turnover is still useful in improving long-term bone health in kidney graft recipients remains unclear in this study. In contrast, Haas *et al.* [51], who investigated the efficacy of intravenous zoledronate (at engraftment and after 3 months) in this setting, found no increased rate of adynamic bone disease in biopsies of bisphosphonate treated transplant patients compared to controls.

Unlike the previously mentioned studies, oral bisphosphonate intake was investigated recently by Torregrosa *et al.* [53], who demonstrated that weekly administration of risedronate is also well-tolerated and effective in improving BMD and bone pain in renal graft recipients with established osteoporosis.

Thus, bisphosphonate therapy may be beneficial to counterbalance the substantial bone loss occurring within the first months after renal transplantation. However, the potential induction of adynamic or low turnover bone disease needs to be considered in the decision of its use in each patient individually.

A systematic review of randomized controlled trials published in 2007 by Palmer *et al.* [54] analyzed the efficacy of various agents for preventing bone loss in renal graft recipients, including bisphosphonates, vitamin D analogues and calcitonin. The treatment effects were compared to one another and with a control group receiving no bone sparing therapy. Twenty-four trials were

included; none of them was powered to demonstrate a treatment-related reduction in fracture risk at any site after transplantation.

Palmer *et al.* primarily included all reports investigating the effect of bisphosphonates on post-transplant bone loss, in addition to the studies on de novo renal graft recipients. Nevertheless, the results were similar to the above discussed analysis with a significant improvement in femoral neck and lumbar spine BMD after bisphosphonate therapy. Again, the intervention was not associated with a reduction in fracture risk. An interesting finding, however, was the significantly lower risk of acute transplant rejections in bisphosphonate treated patients (three trials including 108 patients: RR 0.59, $P = 0.01$). An immunoinhibitory effect was already shown *in vitro* for alendronate, where it interfered with the T-cell function by inhibiting antigen-presenting cells [55]; and the ability to reduce the incidence of acute rejections was supported by data of various animal studies [56].

Apart from the bisphosphonates versus control analysis, only few randomized controlled trials were available for the other summary estimates in Palmer's systematic review. Considering the small sample size of those studies, the power of the pooled analyses is limited. Two trials including 51 patients delivered extractable data to investigate the effect of calcitriol on bone density development [57,58]. Compared with no treatment, the pooled results showed a beneficial effect of this intervention on BMD at lumbar spine and femoral neck. However, when compared head-to-head, bisphosphonates had greater efficacy to preserve BMD than vitamin D sterols, particularly at the lumbar spine.

As data on calcitonin therapy following renal transplantation are limited, only the controlled study by Grotz *et al.* was discussed in Palmer's meta-analysis concerning the effect on percentage change in BMD. The authors compared nasal calcitonin (200 IU for 2 weeks every 3 months) with clodronate (800 mg/day) and no bone sparing therapy in long-term graft recipients [59]. Compared to controls, treatment with calcitonin resulted in a significant improvement in percentage change of BMD at the lumbar spine, but not at the femoral neck. No significant differences regarding BMD outcomes or fracture risk were noticed between calcitonin and bisphosphonate treated subjects.

Whereas no individual therapeutic intervention (bisphosphonates, vitamin D sterol or calcitonin) in Palmer's meta-analysis led to a decrease in fracture risk compared to control, the combined analysis of any intervention showed a modest reduction in the relative risk of fractures by 49% after 6–12 months of treatment. This finding depended on the number of patients in this combined analysis allowing adequate power to determine a change in fracture rate between any treatment and placebo/no treatment.

Comparable findings regarding bone density, as already discussed, were recently reported in a prospective study of 60 renal graft recipients, who were randomly assigned to alfacalcidiol (0.5 μg/day), alendronate (5 mg/day), calcitonin (200 mg every other day) or a control group, with all patients also receiving oral calcium carbonate (500 mg/day) [60]. At 12-month post-transplant, the changes in lumbar spine BMD were +2.1%, +0.8%, +1.7% and −3.2%, in the study groups. At femoral neck, the corresponding values were +1.8%, +0.6%, +1.6% and −3.8%. Thus, early post-transplant bone loss was similarly prevented by alfacalcidiol, alendronate and calcitonin, while sole calcium supplementation had no bone sparing effect.

Further therapeutic options under investigation

Antiresorptive agents such as bisphosphonates can help restore skeletal balance by reducing bone turnover. Another therapeutic approach is to enhance bone formation. The anabolic effects of intermittently administrated recombinant PTH (rPTH) on bone have been shown in the general population. In a study of postmenopausal women, teriparatide [PTH (1–34)], administered as a 20 μg daily subcutaneous injection, increased vertebral BMD by 9% and femoral BMD by 3% during 21 months of follow-up [61]. There was an associated 65% reduction in the incidence of vertebral fractures and a 54% reduction at nonvertebral sites. Recently, Haas *et al.* primarily investigated the influence of 20 μg teriparatide on bone mass development early after renal engraftment [62]. Six months post-transplant, radial and lumbar spine BMD remained unchanged in rPTH as well as placebo treated subjects. At femoral neck, bone density remained stable in the teriparatide group, but decreased in the control group. The authors summarized that teriparatide showed no relevant additive bone sparing effect to a treatment with vitamin D plus calcium, which was administered to all recipients; probably because of a persistent PTH resistance of the bone in the early post-transplant period.

During the last years, the calcimimetic agent cinacalcet was evaluated for the treatment of hypercalcemia in renal graft patients with ongoing secondary hyperparathyroidism. As shown in several post-transplant trials, cinacalcet successfully reduced elevated serum calcium and PTH levels with no negative effect on renal function [63,64]. In consideration of the fact that efforts to prevent post-transplant ROP with calcitriol may be limited by hypercalcemia and bisphosphonates may increase the risk of adynamic bone disease, calcimimetics offer an option of suppressing PTH secretion and possibly mitigating the systemic and skeletal complications of hyperparathyroid-

ism. As far as we know, however, no study has been published up to now assessing the effects of calcimimetics on BMD and bone histology in the renal transplant population. A recently published paper by Borchhardt *et al.* [45] reported about biopsy proven low turnover ROP in nearly 50% of renal graft recipients with hypercalcemia and post-transplant hyperparathyroidism. Hence, lowering PTH by cinacalcet may further enhance adynamic bone disease in this substantial number of patients.

References

1. Cohen A, Shane E. Osteoporosis after solid organ and bone marrow transplantation. *Osteoporos Int* 2003; **14**: 617.
2. Hruska KA, Teitelbaum SL. Renal osteodystrophy. *N Engl J Med* 1995; **333**: 166.
3. Iwasaki Y, Yamato H, Nii-Kono T, *et al.* Insufficiency of PTH action on bone in uremia. *Kidney Int Suppl* 2006; **70**: S34.
4. Kodras K, Haas M. Effect of kidney transplantation on bone. *Eur J Clin Invest* 2006; **36**(Suppl. 2): 63.
5. Brandenburg VM, Ketteler M, Fassbender WJ, *et al.* Development of lumbar bone mineral density in the late course after kidney transplantation. *Am J Kidney Dis* 2002; **40**: 1066.
6. Brandenburg VM, Politt D, Ketteler M, *et al.* Early rapid loss followed by long-term consolidation characterizes the development of lumbar bone mineral density after kidney transplantation. *Transplantation* 2004; **77**: 1566.
7. Pichette V, Bonnardeaux A, Prudhomme L, Gagne M, Cardinal J, Ouimet D. Long-term bone loss in kidney transplant recipients: a cross-sectional and longitudinal study. *Am J Kidney Dis* 1996; **28**: 105.
8. Grotz WH, Mundinger FA, Rasenack J, *et al.* Bone loss after kidney transplantation: a longitudinal study in 115 graft recipients. *Nephrol Dial Transplant* 1995; **10**: 2096.
9. Grotz WH, Mundinger FA, Gugel B, Exner V, Kirste G, Schollmeyer PJ. Bone fracture and osteodensitometry with dual energy X-ray absorptiometry in kidney transplant recipients. *Transplantation* 1994; **58**: 912.
10. Ramsey-Goldman R, Dunn JE, Dunlop DD, *et al.* Increased risk of fracture in patients receiving solid organ transplants. *J Bone Miner Res* 1999; **14**: 456.
11. Nisbeth U, Lindh E, Ljunghall S, Backman U, Fellstrom B. Increased fracture rate in diabetes mellitus and females after renal transplantation. *Transplantation* 1999; **67**: 1218.
12. Durieux S, Mercadal L, Orcel P, *et al.* Bone mineral density and fracture prevalence in long-term kidney graft recipients. *Transplantation* 2002; **74**: 496.
13. Schott AM, Hans D, Duboeuf F, *et al.* Quantitative ultrasound parameters as well as bone mineral density are better predictors of trochanteric than cervical hip fractures in elderly women. Results from the EPIDOS study. *Bone* 2005; **37**: 858.
14. Grotz WH, Mundinger FA, Muller CB, *et al.* Trabecular bone architecture in female renal allograft recipients – assessed by computed tomography. *Nephrol Dial Transplant* 1997; **12**: 564.
15. Mikuls TR, Julian BA, Bartolucci A, Saag KG. Bone mineral density changes within six months of renal transplantation. *Transplantation* 2003; **75**: 49.
16. Canalis E, Delany AM. Mechanisms of glucocorticoid action in bone. *Ann N Y Acad Sci* 2002; **966**: 73.
17. Canalis E. Mechanisms of glucocorticoid-induced osteoporosis. *Curr Opin Rheumatol* 2003; **15**: 454.
18. Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. *Ann Intern Med* 1990; **112**: 352.
19. Aroldi A, Tarantino A, Montagnino G, Cesana B, Cocucci C, Ponticelli C. Effects of three immunosuppressive regimens on vertebral bone density in renal transplant recipients: a prospective study. *Transplantation* 1997; **63**: 380.
20. Nowacka-Cieciura E, Durlik M, Cieciura T, *et al.* Positive effect of steroid withdrawal on bone mineral density in renal allograft recipients. *Transplant Proc* 2001; **33**: 1273.
21. van den Ham EC, Kooman JP, Christiaans ML, van Hooff JP. The influence of early steroid withdrawal on body composition and bone mineral density in renal transplantation patients. *Transpl Int* 2003; **16**: 82.
22. McIntyre HD, Menzies B, Rigby R, Perry-Keene DA, Hawley CM, Hardie IR. Long-term bone loss after renal transplantation: comparison of immunosuppressive regimens. *Clin Transplant* 1995; **9**: 20.
23. Movsowitz C, Epstein S, Fallon M, *et al.* Cyclosporin-A in vivo produces severe osteopenia in the rat: effect of dose and duration of administration. *Endocrinology* 1988; **123**: 2571.
24. Schlosberg M, Movsowitz C, Epstein S, Ismail F, Fallon MD, Thomas S. The effect of cyclosporin A administration and its withdrawal on bone mineral metabolism in the rat. *Endocrinology* 1989; **124**: 2179.
25. Orcel P, Denne MA, de Vernejoul MC. Cyclosporin-A in vitro decreases bone resorption, osteoclast formation, and the fusion of cells of the monocyte-macrophage lineage. *Endocrinology* 1991; **128**: 1638.
26. Epstein S. Post-transplantation bone disease: the role of immunosuppressive agents and the skeleton. *J Bone Miner Res* 1996; **11**: 1.
27. Monegal A, Navasa M, Guanabens N, *et al.* Bone mass and mineral metabolism in liver transplant patients treated with FK506 or cyclosporine A. *Calcif Tissue Int* 2001; **68**: 83.
28. Goffin E, Devogelaer JP, Lalaoui A, *et al.* Tacrolimus and low-dose steroid immunosuppression preserves bone mass after renal transplantation. *Transpl Int* 2002; **15**: 73.

29. Julian BA, Quarles LD, Niemann KM. Musculoskeletal complications after renal transplantation: pathogenesis and treatment. *Am J Kidney Dis* 1992; **19**: 99.
30. Torres A, Rodriguez AP, Concepcion MT, *et al.* Parathyroid function in long-term renal transplant patients: importance of pre-transplant PTH concentrations. *Nephrol Dial Transplant* 1998; **13**(Suppl. 3): 94.
31. Koch Nogueira PC, David L, Cochat P. Evolution of secondary hyperparathyroidism after renal transplantation. *Pediatr Nephrol* 2000; **14**: 342.
32. Drueke TB. Cell biology of parathyroid gland hyperplasia in chronic renal failure. *J Am Soc Nephrol* 2000; **11**: 1141.
33. Reinhardt W, Bartelworth H, Jockenhovel F, *et al.* Sequential changes of biochemical bone parameters after kidney transplantation. *Nephrol Dial Transplant* 1998; **13**: 436.
34. Torres A, Machado M, Concepcion MT, *et al.* Influence of vitamin D receptor genotype on bone mass changes after renal transplantation. *Kidney Int* 1996; **50**: 1726.
35. Torregrosa JV, Campistol JM, Montesinos M, Pons F, Martinez de Osaba MJ. Evolution of bone mineral density after renal transplantation: related factors. *Nephrol Dial Transplant* 1995; **10**(Suppl. 6): 111.
36. Heaf J, Tvedegaard E, Kanstrup IL, Fogh-Andersen N. Hyperparathyroidism and long-term bone loss after renal transplantation. *Clin Transplant* 2003; **17**: 268.
37. Carlini RG, Rojas E, Weisinger JR, *et al.* Bone disease in patients with long-term renal transplantation and normal renal function. *Am J Kidney Dis* 2000; **36**: 160.
38. Cueto-Manzano AM, Konel S, Hutchison AJ, *et al.* Bone loss in long-term renal transplantation: histopathology and densitometry analysis. *Kidney Int* 1999; **55**: 2021.
39. Casez JP, Lippuner K, Horber FF, Montandon A, Jaeger P. Changes in bone mineral density over 18 months following kidney transplantation: the respective roles of prednisone and parathyroid hormone. *Nephrol Dial Transplant* 2002; **17**: 1318.
40. Cueto-Manzano AM, Freemont AJ, Adams JE, Mawer B, Gokal R, Hutchison AJ. Association of sex hormone status with the bone loss of renal transplant patients. *Nephrol Dial Transplant* 2001; **16**: 1245.
41. Brandenburg VM, Ketteler M, Heussen N, *et al.* Lumbar bone mineral density in very long-term renal transplant recipients: impact of circulating sex hormones. *Osteoporos Int* 2005; **16**: 1611.
42. Kwan JT, Almond MK, Evans K, Cunningham J. Changes in total body bone mineral content and regional bone mineral density in renal patients following renal transplantation. *Miner Electrolyte Metab* 1992; **18**: 166.
43. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; **42**: S1.
44. Schwarz C, Sulzbacher I, Oberbauer R. Diagnosis of renal osteodystrophy. *Eur J Clin Invest* 2006; **36**(Suppl. 2): 13.
45. Borchhardt K, Sulzbacher I, Benesch T, Fodinger M, Sunder-Plassmann G, Haas M. Low-turnover bone disease in hypercalcemic hyperparathyroidism after kidney transplantation. *Am J Transplant* 2007; **7**: 2515.
46. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.8. Bone disease. *Nephrol Dial Transplant* 2002; **17**(Suppl. 4): 43.
47. Mitterbauer C, Schwarz C, Haas M, Oberbauer R. Effects of bisphosphonates on bone loss in the first year after renal transplantation – a meta-analysis of randomized controlled trials. *Nephrol Dial Transplant* 2006; **21**: 2275.
48. Coco M, Glicklich D, Faugere MC, *et al.* Prevention of bone loss in renal transplant recipients: a prospective, randomized trial of intravenous pamidronate. *J Am Soc Nephrol* 2003; **14**: 2669.
49. Grotz W, Nagel C, Poeschel D, *et al.* Effect of ibandronate on bone loss and renal function after kidney transplantation. *J Am Soc Nephrol* 2001; **12**: 1530.
50. Fan SL, Almond MK, Ball E, Evans K, Cunningham J. Pamidronate therapy as prevention of bone loss following renal transplantation1. *Kidney Int* 2000; **57**: 684.
51. Haas M, Leko-Mohr Z, Roschger P, *et al.* Zoledronic acid to prevent bone loss in the first 6 months after renal transplantation. *Kidney Int* 2003; **63**: 1130.
52. Kovac D, Lindic J, Kandus A, Bren AF. Prevention of bone loss with alendronate in kidney transplant recipients. *Transplantation* 2000; **70**: 1542.
53. Torregrosa JV, Fuster D, Pedroso S, *et al.* Weekly risedronate in kidney transplant patients with osteopenia. *Transpl Int* 2007; **20**: 708.
54. Palmer SC, McGregor DO, Strippoli GF. Interventions for preventing bone disease in kidney transplant recipients. *Cochrane Database Syst Rev* 2007; **3**: CD005015.
55. Sansoni P, Passeri G, Fagnoni F, *et al.* Inhibition of antigen-presenting cell function by alendronate in vitro. *J Bone Miner Res* 1995; **10**: 1719.
56. Fryer J, Grant D, Jiang J, *et al.* Influence of macrophage depletion on bacterial translocation and rejection in small bowel transplantation. *Transplantation* 1996; **62**: 553.
57. Koc M, Tuglular S, Arikan H, Ozener C, Akoglu E. Alendronate increases bone mineral density in long-term renal transplant recipients. *Transplant Proc* 2002; **34**: 2111.
58. Nam JH, Moon JI, Chung SS, *et al.* Pamidronate and calcitriol trial for the prevention of early bone loss after renal transplantation. *Transplant Proc* 2000; **32**: 1876.
59. Grotz WH, Rump LC, Niessen A, *et al.* Treatment of osteopenia and osteoporosis after kidney transplantation. *Transplantation* 1998; **66**: 1004.
60. El-Agroudy AE, El-Husseini AA, El-Sayed M, Mohsen T, Ghoneim MA. A prospective randomized study for prevention of postrenal transplantation bone loss. *Kidney Int* 2005; **67**: 2039.

61. Neer RM, Arnaud CD, Zanchetta JR, *et al.* Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001; **344**: 1434.
62. Cejka D, Kodras K, Benesch T, *et al.* Effekte von rekombinantem Parathormon auf den Knochenverlust nach Nierentransplantation. *Journal für Mineralstoffwechsel* 2007; **14**(abstract): 175.
63. Bergua C, Torregrosa JV, Cofan F, Oppenheimer F. Cinacalcet for the treatment of hypercalcemia in renal transplanted patients with secondary hyperparathyroidism. *Transplant Proc* 2007; **39**: 2254.
64. Srinivas TR, Schold JD, Womer KL, *et al.* Improvement in hypercalcemia with cinacalcet after kidney transplantation. *Clin J Am Soc Nephrol* 2006; **1**: 323.

