

Treatment of bone disease in renal transplant recipients

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ABSTRACT

Posttransplantational bone disease is a multifactorial, complex condition, to which both pre-existing renal osteodystrophy and factors emerging after renal transplantation contribute significantly. Among the latter the application of glucocorticoids is considered to play an outstanding pathophysiological role. Posttransplantational bone disease potentially never resolves completely. The two central features of this condition are a rapid and accelerated bone loss as well as a significant elevation of the fracture risk. Therefore, prevention and treatment are mandatory. Vitamin D, the active metabolites

and the bisphosphonates are currently the most extensively tested agents for the treatment of renal posttransplantational bone disease. However, the most appropriate therapeutic strategies still need to be determined and it is yet unproven that any medical intervention reduces the fracture risk in renal transplant recipients.

Key-words: Alendronate; bone loss; bone mineral density; renal transplantation; treatment; vitamin D.

INTRODUCTION

Since the disturbances of bone metabolism after renal transplantation are complex and multifactorial the commonly used term "posttransplantational osteoporosis"¹ should be replaced by a more appropriate nomenclature such as posttransplantational bone disease or

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posttransplantational osteopathy². The two outstanding sequelae of this condition are a rapid and accelerated bone loss as well as a significant elevation in the fracture risk³⁻⁶. While the former is pronounced during the first year after transplantation⁷ and may result in a bone mineral density decrease exceeding 10% within 6 months⁶, the latter is a cumulative problem over years. Steroid application is the most important single contributor in the development of posttransplantational bone disease^{3,6,8}. Bone disease contributes significantly to increased morbidity and may even have some impact on mortality in renal transplant recipients⁹. Therefore, this issue should be a major focus of the nephrologist's care for transplant recipients⁶.

The chance of complete reversibility of osseous disturbances in renal allograft recipients is limited by 1) incomplete restoration of renal function or the development of graft failure and 2) by the chronic administration of drugs that interact negatively with bone metabolism (e.g. immunosuppressants).

THERAPEUTIC OPTIONS IN POSTTRANSPLANTATIONAL BONE DISEASE

Compared to the evidence in case of the treatment of postmenopausal osteoporosis, for which several level 1 recommendations from large, randomized, placebo-controlled trials are available ("American association of clinical endocrinologists: www.aace.com), the evidence for any treatment modality for the accelerated posttransplantational bone loss is much less extensive⁶. The main reasons for this discrepancy is the generally low power of the available "bone trials" in renal transplant recipients. The cumulative number of participants reported so far is only approximately 1000 with single

studies only exceptionally exceeding 100 patients, the study duration rarely exceeded 12 months and only bone mineral density development – not fracture incidence – was the primary endpoint⁶. Consequently, the following guidelines for medical intervention in posttransplantational bone disease are a mixture of preliminary conclusions from the therapy data presently available in renal transplant recipients⁶, of opinion-based recommendations¹⁰ and very importantly of conclusions by analogy derived from our therapeutic knowledge concerning bone disease in chronic renal insufficiency¹⁰, postmenopausal osteoporosis (www.aace.com), and glucocorticoid-induced osteoporosis (www.rheumatology.org). No medication has the official approval for posttransplantational bone disease ("off-label use"). Summarizing all these sources the evidence is currently best for the use of vitamin D, the active vitamin D metabolites, and bisphosphonates⁶. Other substances hold promise in special situations but data in renal transplant recipients are not yet available [e.g. PTH(1-34) to burst the impasse of adynamic bone disease or raloxifene to reduce the extraordinary cardiovascular risk; see the ongoing *Raloxifene use for the Heart (RUTH)* trial].

VITAMIN D THERAPY

The K/DOQI 2003 guidelines explicitly recommend to orient the therapy of posttransplantational bone disease towards the guidelines for treatment of bone disease in chronic renal insufficiency¹⁰.

Oral vitamin D plus calcium is effective in the reduction of the postmenopausal osteoporotic fracture risk^{11,12} and vitamin D, calcitriol and alfalcidol are evidence-based recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis

(www.rheumatology.org). Therefore, vitamin D (cholecalciferol or ergocalciferol) is the basis of treatment for posttransplantational bone disease especially taking into account that many patients chronically receive glucocorticoids.

According to the K/DOQI guidelines vitamin D (800IE per day) plus calcium (1000-1500mg per day) supplementation should be administered in patients with chronic kidney disease (CKD) stage 2 (glomerular filtration rate, GFR > 60 ml/min) and insufficient (16-30 ng/mL) or deficient (<15 ng/mL) serum calcidiol levels to prevent and treat hyperparathyroidism. Its active metabolites calcitriol (0.25-0.5 µg/day) and alfacalcidol (0.25-0.5 µg/day) are preferred in stage 3 (GFR 30-59 ml/min) and stage 4 (15 – 29 ml/min) renal disease¹⁰. Prerequisites for the administration of calcitriol and alfacalcidol are calcidiol levels > 30 ng/mL and iPTH levels not falling below the individual target range (CKD stage 3: 35-70 pg/mL, CKD stage 4: 70 – 110 pg/mL)¹⁰. Additional, prerequisites for the administration of vitamin D and the active sterols are the absence of hypercalcemia and a controlled calcium×phosphate product (corrected total calcium <9.5mg/dL and phosphate < 4.6 mg/dL)¹⁰.

Calcitriol and alfacalcidol have been shown to reduce the extent of early posttransplant bone loss at the lumbar spine and femoral neck compared to placebo^{13,14}. However, only one very small study (24 renal transplant recipients)¹⁵ found a significant increase of posttransplant bone density after 12 months of calcitriol treatment. Besides the potential increase in the calcium×phosphate product, additional harmful side-effects of vitamin D treatment (especially with active forms) are the deterioration of renal function, the induction of extraosseous calcifications and the suppression of the bone metabolism towards adynamic bone disease^{10,16}. All renal transplant recipients should be treated according to the recommendations mentioned

above with vitamin D or active metabolites plus calcium except for those with one or more of the above-listed contraindications. In that case the dosage of vitamin D or its metabolites should be reduced or the application should be stopped¹⁰. The potential benefits of vitamin D derivatives (doxercalciferol, paricalcitol) in terms of bone strength in renal transplant recipients are currently undetermined.

BISPHOSPHONATES

Alendronate is the most extensively investigated bisphosphonate in posttransplantational bone disease⁶. A dosage of 10 mg alendronate per day significantly increased the lumbar and femoral BMD within 12 months compared to baseline (between 3.4% to 8.2% for the lumbar spine and 1.6% to 9.3% for the femoral neck)^{15,17,18}. In terms of BMD increase alendronate was superior to vitamin D or calcitriol^{15,18,19}, while intravenous pamidronate did not result in a significant BMD increase in renal transplant recipients²⁰⁻²². Taking into account these data and the effectiveness of alendronate in other forms of osteoporosis²³⁻²⁵, it should currently be regarded as the first choice bisphosphonate for posttransplantational bone disease. Risedronate – the second first-line bisphosphonate for postmenopausal osteoporosis – has not yet been evaluated in renal transplant recipients.

Several concerns limit the widespread and unreflected use of bisphosphonates in renal transplant recipients. Among these renal toxicity²⁶⁻²⁸ and the threat of adynamic bone disease need to be especially emphasized²⁰. Therefore, alendronate administration should be restricted to transplant recipients with a high fracture risk but with stable transplant function (GFR > 50-60 mL/min)²⁷ and without signs of bone metabolism oversuppression⁶. Intact PTH levels may

help to exclude adynamic bone disease in patients with CKD¹⁰ but in view of its low sensitivity bone histomorphometry may be required in many cases of doubt²⁹. One or several of the following criteria define a patient at risk^{10,27}: patients with previous fractures, with very low bone density (T-score <2.0), with combined kidney-pancreas transplantation, diabetics and postmenopausal women.

In our opinion two other conditions should be added to the list of bisphosphonate indications: First, a pronounced derangement of the calcium×phosphate product caused by vitamin D treatment. *In vivo* data show that switching to bisphosphonates in the latter setting might be helpful in preventing extraosseous calcifications³⁰. Second, a rapid and pronounced bone loss early after transplantation requires fast acting and effective medical intervention. In order to initiate therapy early enough, a DEXA scan should be performed at six months posttransplant to identify “fast losers”.

AREAS OF UNCERTAINTY

Among many open questions regarding the optimization of posttransplantational bone disease treatment three issues warrant special attention: First it urgently needs to be proven, that any therapy strategy reduces the fracture risk in these patients – a decisive question in view of the fact, that the BMD is only a weak predictor of the fracture risk in patients with CKD²⁶. Second, it is currently impossible to establish an active treatment strategy for patients with adynamic bone disease. Third, closely linked to the first two issues is the uncertainty concerning the necessary duration of therapy. Initiation of treatment appears most promising at the time when bone mass is reduced most rapidly, i.e. within the first 12 months after renal

transplantation. On the other hand some data in long-term renal transplant recipients indicate that posttransplantational bone loss is possibly a creeping and chronic condition requiring long-term intervention³¹ that conversely increases the risk of deleterious side-effects of active therapy (renal toxicity, extraosseous calcification, adynamic bone disease etc.).

The following section presents a summary on current treatment recommendations for posttransplantational bone disease (modified after^{10,27}).

- Consequent control of pretransplant bone disease; both adynamic bone disease and overt osteitis fibrosa should be avoided¹⁰.
- Optimize vitamin D status after transplantation²⁷.
- Recommend calcium intake of 1000-1500 mg/day²⁷, avoid hypercalcemia.
- Use of bisphosphonates (alendronate) recommended for patients at risk^{10,27}: T-score <2.0, patients with previous osteoporotic fractures, diabetics, patients after combined kidney-pancreas transplantation and postmenopausal women. We recommend to perform a DEXA at 6 months posttransplant in order to identify “fast losers”. Alendronate application in patients with a glomerular filtration rate <50 ml/min (or creatinine > 160µmol/L) in patients with adynamic bone disease is not recommended.
- Consider calcitonin, if vitamin D and bisphosphonates are not appropriate^{10,27} (e.g. 200U calcitonin/day).
- Restore normal gonadal^{10,27} and thyroid function if necessary²⁷.
- Treat uncontrolled persistent hyperparathyroidism²⁷ but avoid parathyroid gland oversuppression.
- Treat persistent severe hypophosphatemia and hypomagnesemia²⁷.

- Use the lowest possible dose of glucocorticoids²⁷.
- Start exercise program, stop smoking (i.e. modulate life-style factors)²⁷.
- Avoid loop diuretics (which induce calciuria)^{10,27}, heparin and other osteoporosis-inducing medications¹⁰.

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