

Mineral and Bone Disease (MBD) on a Kidney Transplant Patient

Doença Mineral e Óssea (DMO) num Transplantado Renal

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■ ABSTRACT

A 50-year-old post-menopausal recipient of a kidney allograft with bone pain, osteoporosis, persistent hypercalcaemia and elevated parathormone (PTH) levels, despite a satisfactory graft function, was treated with bisphosphonates and cinacalcet starting, respectively, 5 and 6 months after renal transplantation (RT). Sixteen months after treatment, there was improvement of bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DEXA). A bone biopsy was taken, unveiling a surprising and worrisome result. Post-RT bone disease is different from classic CKD-MBD and should be managed distinctly, including, in some difficult cases, an invasive evaluation through the performance of a bone biopsy, as suggested in the KDIGO guidelines.

Key Words: Bone biopsy; cinacalcet; ckd-mbd; hypercalcaemia; kidney transplantation; osteoporosis.

■ RESUMO

Uma transplantada renal de 50 anos, pós menopáusicas, com dor óssea, osteoporose, hipercalcemia persistente e níveis elevados de paratormona, apesar de uma razoável função do enxerto renal, foi tratada com bifosfonatos e cinacalcet com início 5 e 6 meses, respectivamente, após a transplantação renal. Verificou-se melhoria da densidade óssea medida por DEXA. Foi realizada uma biópsia óssea que revelou um resultado inesperado e preocupante. A doença óssea após a transplantação renal é diferente da DMO-DRC clássica e deve ser gerida de forma distinta. Nalguns casos, como o ilustrado na presente apresentação, justifica-se o diagnóstico invasivo através do recurso à realização de uma biópsia óssea, como é proposto nas orientações da KDIGO.

Palavras-Chave: Biópsia óssea; cinacalcet; dmo-drc; hipercalcemia; osteoporose; transplantação renal.

INTRODUCTION

The most frequent post-renal transplantation (RT) bone disease is characterized by accelerated loss of bone mineral density and increased risk of fractures. There are no randomized clinical trials in kidney transplant patients examining bone specific therapies on clinical outcomes, such as fractures or cardiovascular disease events. Bone disease in kidney transplant patients is heterogeneous, involving pre-existing renal osteodystrophy, the effects of immunosuppression therapy on bone and the effects of reduced renal function after RT; these factors overlap and result in different pathologic states. Several pharmacologic therapies that target multiple components of the MBD imbalance have been used.

Kidney Disease: Improving Global Outcomes (KDIGO) clinical practical guidelines for the care of kidney transplant recipients includes the management of transplant bone disease. The KDIGO latest guidelines on CKD-MBD were issued in 2009; a conference on controversies on this very issue was announced to be held in October 2013. Its purpose was to evaluate what is known about CKD-MBD, what can be done with what is known and what needs to be learned¹. This case report of hypercalcaemic hyperparathyroidism after RT discloses that urgent need.

CASE REPORT

A 50-year-old white woman was submitted to RT in October 2009. Her immunosuppression consisted of basiliximab (first and fourth RT days), methylprednisolone (500-250-125-80 mg in RT days 1-4, respectively), prednisone (35 mg at RT day 5, followed by progressive tapering until 5 mg at RT day 30), tacrolimus and mycophenolate mofetil. She had autosomal dominant polycystic kidney disease and had been on haemodialysis since January 2005. Prior to RT there was a long history of symptomatic herniated vertebral disc; she was referred to Neurosurgery, but only functional rehabilitation was recommended. She had no other relevant comorbidity. Age of menarche was 13 years, with spontaneous menopause at age 47. She was slightly overweight (body mass index 27) and a non-smoker.

While on haemodialysis, the patient's mineral serum values were remarkable for hyperphosphatemia,

with phosphorus ranging 4.1-7.1 mg/dl, calcium 8.0-9.9 mg/dl, calcium-phosphorus product 35-61 (mg/dl)² and intact parathormone (iPTH) between 108-170 pg/ml. She was on sevelamer 800 mg, 6 to 9 pills qd and calcium carbonate 1000 mg 3 to 6 pills qd for over three years; no vitamin D or calcimimetic were taken.

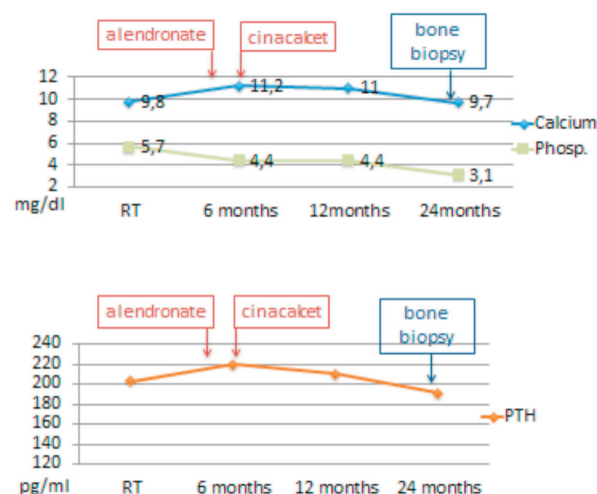
Five months after RT her gynaecologist found she had reduced BMD: a dual-energy x-ray absorptiometry (DEXA) revealed lumbar spine osteoporosis (T-score -2.5 SD) and femoral neck osteopenia (T-score -2.1 SD). He prescribed alendronic acid 70 mg every week.

Six months after RT, the patient maintained reasonable kidney graft function, with a serum creatinine of 1.1 mg/dl (estimated glomerular filtration rate by CKD-EPI Creatinine Equation of 59 ml/min/1.73m²). She had persistent moderate hyperparathyroidism (iPTH 220 pg/ml) and hypercalcaemia (maximum 11.4 mg/dl). Cinacalcet was then initiated, 30 mg po qd. Plasma calcium levels slightly decreased, without a significant PTH levels change (190-210 pg/ml) (Graphics I and II).

Eight months after RT she suffered a traumatic hip fracture.

Graphics I and II

Laboratory serum values of calcium and phosphorus (Table I) and iPTH (Table II) at the time of RT, 6, 12 and 24 months after RT.



Twenty-two months after RT a new DEXA-scan showed a significant increase of femoral neck bone density (T-score -1.5 SD), compared with the previous exam; lumbar spine density was similar (T-score -2.6 SD).

During all RT period, the patient continued to suffer widespread bone pain, mostly lumbar pain, which she recognized as a consequence of the degenerative bone disease identified well before RT. This clinical condition interfered markedly with her well-being, not only because of the psychological distress associated with constant pain, but also by the progressively compromised physical activity. Besides that, this period had been unremarkable, despite a fall that resulted in the bone fracture previously referred and some minor urinary tract infections.

Two years after RT (at the 23rd month), a bone biopsy was performed (Fig. 1). Serum PTH was still elevated at 191 pg/ml; calcium, phosphorus and alkaline phosphatase were within normal values; 25-hydroxy vitamin D level was 41.3 nmol/L (normal values 75-250 nmol/L); thyroid blood tests were normal. The biopsy revealed severe osteoporosis and adynamic bone disease ("Frozen Bone"), with normal bone mineralization. The patient maintained satisfactory graft function (serum creatinine 0.9-1.2 mg/dl).

Alendronate and cinacalcet were immediately discontinued and cholecalciferol (1.334 IU of vitamin

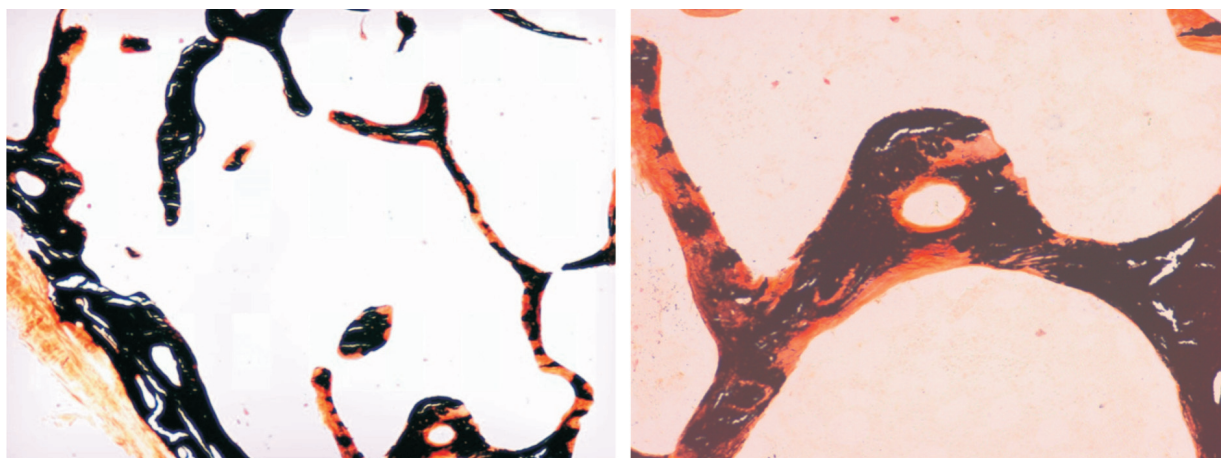
D₃ per day) was added. A few weeks later, the patient felt quite better, with bone pain remission and physical activity resumed. Weight-bearing physical activity was encouraged, and she started gymnastic classes with great physical improvement. Her most recent relevant serum laboratory values, 10 months after the bone biopsy, are creatinine 1.19 mg/dl, calcium 11.1 mg/dl, phosphorus 2.5 mg/dl, PTH 139.5 pg/ml. She has a vascular calcification Adragão score of 0 / 8 (no vascular calcification observed on pelvis and hand plain x-ray) and a Kauppila score of 2 / 24 (vascular calcification on abdominal aorta seen on lateral abdomen plain x-ray.)

DISCUSSION

We report a case of CKD-MBD in a post-menopausal kidney transplant recipient (after almost 5 years on haemodialysis), who had lumbar spine osteoporosis and femoral osteopenia with eGFR around 60 mL/min/1.73m², treated with bisphosphonates to whom, in face of persistent hypercalcaemia and hyperparathyroidism, cinacalcet was added. Skeletal history was significant for pre-RT symptomatic herniated vertebral disc and progressive disabling bone pain thereafter. Hypercalcaemia came to normal values and PTH remained high. Meanwhile, a (traumatic)

Figure 1

Transiliac crest bone biopsy with doxycycline labeling and histomorphometric analysis: absent active osteoblasts; intense reduction of cortical bone and trabecular volume: severe osteoporosis in the context of adynamic disease.



bone fracture occurred. She maintained reasonable good graft function and bone density (by DEXA scan) was ameliorated, but her symptoms did not improve. A bone biopsy was diagnostic for adynamic bone disease.

This case illustrates the mandatory use of bone histomorphology to manage BMD in RT patients. The risks associated with bisphosphonates and calcimimetics on RT, despite good graft function, are enlightened here; although prescribed according to prevailing recommendations, their use resulted in unwanted clinical consequences.

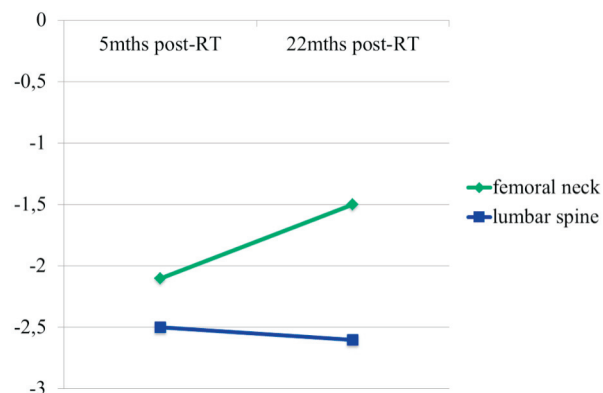
■ Low bone mineral density

Post-RT bone disease comprises a spectrum of metabolic alterations of bone remodelling that include pre-existing renal osteodystrophy alterations, as well as new factors that occur after transplantation, being influenced by immunosuppressive therapy, kidney transplant function, hypophosphatemia, and disturbances in the fibroblastic growth factor 23-PTH-vitamin D axis^{2,3}. Many studies in transplant recipients have shown a negative correlation between glucocorticoid cumulative dose and BMD. The mechanisms whereby glucocorticoids may affect bone metabolism are multifactorial; these drugs increase osteoclastic resorption, decrease osteoblastic activity and promote osteoblast apoptosis; they also may indirectly affect bone metabolism by decreasing intestinal calcium absorption and increasing renal calcium wasting, leading to increased PTH secretion. Secondary hypogonadism further reduces bone formation^{3,4}. The role of calcineurin inhibitors regarding rates of bone mass loss is less clear and limited information is available on mycophenolate mofetil or basiliximab. Our patient did not have a high cumulative glucocorticoid dose, although she was not on a corticoid-sparing regimen; she also had the physiologic decrease in gonadal steroids that is associated with menopause. Pre-RT osteodystrophy (with iPTH in the low/normal range), highly daily calcium carbonate over that period (3 to 6 grams), corticosteroid use, hypogonadal state, bisphosphonate and cinacalcet therapy likely contributed to her adynamic bone disease.

Accelerated loss of bone density occurs in the first year after RT, mainly in the first 3 to 6 months; after the first year, studies are conflicting⁵⁻⁹. The use

Graphics III

Percentage change in vertebral bone mineral density.



of bisphosphonates post-transplantation has been shown to prevent loss or increase BMD¹⁰⁻¹⁵. However, there has generally been no evidence of fracture reduction¹⁶, and bisphosphonate treatment carries the risk of inducing or prolonging adynamic bone disease in the presence of renal dysfunction¹⁷. Bisphosphonate deposition in the bone mineralization can last 10 years, as emphasized in a recent review by Susan Ott¹⁸. This long deposition and the interference with bone remodelling should be taken into account before the initiation of this therapy. As these drugs are eliminated (almost exclusively) by the kidney, renal function after kidney transplantation has also to be considered.

In this patient, the bisphosphonates prescribed by the gynaecologist for osteoporosis treatment potentially could lower serum calcium concentration, but hypercalcaemia persisted. In face of persistent hypercalcaemia with elevated PTH, cinacalcet was introduced. Several small studies showed that cinacalcet was able to lower the serum calcium, with no significant change in the PTH values¹⁹⁻²¹.

BMD provides no information regarding bone quality, bone mineralization, bone architecture or turnover in RT population²². Nevertheless, KDIGO suggests to measure BMD in the first 3 months after RT when patients have GFR > 30 mL/min/1.73m² (evidence grade 2D) and, when low, to consider treatment with vitamin D, calcitriol/alfacalcidol or bisphosphonates (evidence grade 2C). They also refer that treatment choices may

be influenced by the presence of CKD-MBD, as indicated by abnormal levels of calcium, phosphorus, PTH, alkaline phosphatases and 25(OH)vitamin D. KDIGO guidelines also defend that it is reasonable to consider the need to perform a bone biopsy to guide treatment (*Not Graded*)²³. The Spanish Nephrology Society guidelines launched 2 years ago go even further on that issue: they recommend a DEXA scan to kidney recipients with fracture risk and, if it reveals osteoporosis and PTH is > 60 pg/ml, to start bisphosphonates; they also recommend calcimimetics after RT if serum calcium > 10.5 mg/dl and iPTH > 100 pg/ml²⁴. Of note, the KDOQI US commentary on KDIGO guidelines already stated that bisphosphonates should not be used if there are abnormalities in calcium, phosphate, vitamin D, or PTH levels²⁵.

■ Hypercalcaemia

Hypercalcaemia after kidney transplantation is common and often transient in the first 6 months, but cannot fade away in some patients. Tubulointerstitial calcifications in the kidney graft have been demonstrated in RT patients with high serum PTH and calcium levels in a well-known study, which correlated with an inferior graft outcome one year after transplantation, and hyperparathyroidism and hypercalcaemia were identified as the key factors²⁶. Of note, phosphate supplementation was more prevalent in patients with tubulointerstitial calcifications; moreover, in a subsequent study with 3.5 times more patients, high calcium levels were associated with a reduced risk for allograft loss²⁷.

Usually hypercalcaemia is due to hyperparathyroidism that persists from the previous pre-RT period, and results from the direct effect of PTH in causing calcium efflux from the bone now added to the enhanced renal tubular absorption of calcium by PTH action in the functioning kidney graft, and to the effects of higher levels of calcitriol on the gastrointestinal absorption of calcium by the restoring of 1 α -hydroxylase activity subsequent to functioning nephron mass.

■ Hyperparathyroidism

In up to 50% of transplant recipients, abnormal PTH secretion persists, sometimes causing hypercalcaemia

that may require parathyroidectomy²⁸. Cinacalcet has been shown to correct hypercalcaemia and hyperparathyroidism in several trials in kidney transplant recipients^{19,20,29-36}, however, few of those studies had a control group and none had bone biopsies. One of the concerns with calcimimetics is nephrocalcinosis and graft dysfunction (3 case reports in the literature)³⁷⁻³⁹. In a recent study by Courbebaisse *et al.*, 34 patients received cinacalcet between 3 to 12 months after RT; hypercalciuria was more than twice as high at month 12 as in patients who did not receive cinacalcet treatment, but that was not associated with an increase in calcium deposits on renal biopsies or an alteration of measured GFR³⁰.

Biochemical parameters of bone metabolism, although somewhat useful in monitoring bone health in the non-renal transplant patient, do not predict bone activity or mineralization in the renal transplant recipient, suggesting a skeletal resistance to PTH and eventually also to active vitamin D₃⁴⁰⁻⁴². Nevertheless, some experts suggest that management of post-transplantation bone disease should initially focus on correcting metabolic disorders, using the same principles applied to manage CKD-MBD prior to RT^{2, 23,24}, and consider bone biopsy as an important, yet eventual, additional tool.

The remarkable clinical evolution in this case report, causing high morbidity and affecting the quality of life of this transplant recipient, which greatly improved after changing therapeutic strategy, acknowledges that an improved BMD may not reflect an improvement on bone health. These results also underline that adynamic bone histology may coexist with high iPTH serum levels in the transplanted patients (as already described in the dialysis population^{43,44}).

Recognition of MBD in RT patients as a unique disorder is critical to provide appropriate therapy and avoid iatrogenesis. We believe that the new version of KDIGO guidelines will update current guidelines on this topic.

■ CONCLUSIONS

Especially after RT, biochemical hyperparathyroidism is a complex entity that can be associated

with high or low bone turnover. Treatment of persistent hypercalcaemia according to some prevailing recommendations can lead to, or exacerbate, adynamic bone disease. Presently, it is not known *if* and at what calcium level treatment should be initiated.

In the absence of any randomized controlled trial for the treatment of renal osteodystrophy after RT, it seems wise to begin the therapeutic approach by the correction of deficiency/insufficiency of vitamins, hormones and minerals as we did in the present situation, through the supplementation of cholecalciferol.

Our findings also suggest that before the use of a long acting drug (like bisphosphonates) or an off label drug (like cinacalcet) in a transplanted patient, a bone biopsy should be performed to evaluate bone characteristics: volume, mineralization, quality and architecture (with separation between cortical and trabecular bone).

The presented case draws attention to the fact that we must focus on the trigger event, instead of its manifestations.

Conflict of interest statement: None declared.

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