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ORIGINAL ARTICLE

Post-transplant distal limb syndrome: clinical diagnosis and long-term outcome in 37 renal transplant recipients

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Summary

After the introduction of steroid sparing immunosuppressive protocols, osteonecrosis of the hip has become a rare entity in renal transplantation. Instead, an elusive bilateral pain syndrome of the distal extremities has gained more clinical attention. Because of the typical presentation, it is sometimes referred to as 'post-transplant distal limb syndrome' (PTDLS). The syndrome typically manifests during the first year after transplantation and may lead to significant morbidity because of pain induced immobilization. On MRI-scans, a characteristic bilateral patchy osteoedema can be demonstrated. The etiology of PTDLS has not been determined definitely so far. Over the last 8 years, we have seen the syndrome in 37 out of 639 renal transplant patients (5.8%). There was no association to steroid-medication, age, gender, PTH levels or delayed graft function. As an important finding, we saw a significant rise in alkaline phosphatase from 160 ± 54 to 271 ± 108 U/l ($P = 0.001$) and calcium from 2.46 ± 0.18 to 2.58 ± 0.18 mmol/l ($P = 0.013$) preceding the onset of pain by several weeks. Mean duration of clinical symptoms was 5.1 ± 3.1 months; however, all patients experienced remission without signs of chronic damage on long-term follow up.

Introduction

Renal transplantation has become a routine therapeutic option for end stage renal disease patients. Aseptic necrosis of the femoral head was formerly a feared complication associated with high dose steroids. Following the introduction of steroid sparing immunosuppressive regimens, the incidence of this entity has dropped remarkably [1]. Currently, other less severe but nevertheless clinically important aspects of post-transplant bone disease are to be treated in the transplant unit [2–4]. A rare and often overlooked syndrome is sometimes referred to as 'post-transplant distal limb syndrome' (PTDLS). As the syndrome varies remarkably in severity and presentation, different names have so far been proposed, e.g.: postrenal transplant distal limb bone pain [5], reflex sympathetic dystrophy syndrome [6], calcineurin-inhibitor induced pain syndrome [7] or post-transplant distal-limb bone marrow edema [8]. The syndrome is characteristic of episodes of osteoarticular pain exclusively in the distal lower limbs. The pain typically arises bilaterally and symmetrically within the first year after renal transplantation. It eases on rest and worsens on physical stress sometimes leading in consequence to remarkable morbidity because of immobilization. PTDLS was reported to last weeks or even months, but severe orthopaedic complications have not yet been documented. Although it seems likely to be caused by the calcineurin-inhibitors cyclosporine and tacrolimus (CNI), different etiologies e.g. microfractures have been debated [9–11]. Nevertheless, the definite cause is yet to be elucidated. The incidence of PTDLS seems to vary from 5% to 10% of newly transplanted kidney organ

recipients, but remains probably underestimated to a large extent. On fat-suppressed T2-wheigthed MRI-scans, a typical bilateral bone marrow edema in pain-affected regions of the knees and or feet can be demonstrated [4,7,12]. As another typical feature, the hip regions are exclusively spared. This, as well as the lack of long-term sequelae, at least in our patients, clearly distinguishes PTDLS from steroid-induced aseptic osteonecrosis. The syndrome was first reported in case reports or small cohorts of renal transplant patients on a cyclosporine based immunosuppressive regimen, but was later also described in patients on tacrolimus medication [10,13]. Furthermore, it is not restricted to renal transplant recipients, but was also diagnosed in patients following combined kidney–pancreas, lung and liver transplantation [14]. Switching to a CNI-free immunosuppressive regimen in two patients in a report by Collini *et al.* led to sudden relief of pain, but was associated with an increased risk of graft rejection [7]. We hereby report our experience in diagnosing this rare syndrome in 37 patients and provide long-term follow up data on kidney function and bone outcome in 35 renal allograft recipients with MRI-proven PTDLS.

Patients and methods

Patient characteristics

Over a period of 8 years, 639 patients have received a kidney transplant at our unit. During routine follow-up, PTDLS was diagnosed in 37 patients (5.8% of all transplant recipients). The patient charts were reviewed retrospectively. Mean patient age at diagnosis was 50.4 ± 10.9 years (range 30.6–66.8). Bone marrow edema was diagnosed via MRI on average 5.8 ± 4.8 months (range 1.0–30.0) after renal transplantation. At the time of diagnosis of PTDLS, all patients had a good transplant function with a mean serum creatinine of 1.59 ± 0.40 mg/dl (range 1.00–2.50). 28 patients received a cadaveric organ, five a living genetically unrelated donation and four patients were transplanted following a living related (haplo-identic) kidney donation. 22 patients received calcium-channel blockers (CCB) at the time of diagnosis, a drug class formerly supposed to be protective with regard to the development of bone marrow edema. PTDLS persisted on average 5.1 ± 3.1 months (range 1.0–16.0). In contrast to classical steroid-dependent aseptic necrosis, no patient reported pain in the hip region during rest or physical activity.

Magnetic resonance findings

Typical MRI scans are presented in Fig. 1a–c showing an intense signal in the distal femur condyles as well as the tarsal bones of the feet. In all patients, diagnosis of bone marrow edema was confirmed using either a 1 Teslar (Gyroscan Philips, Eindhoven, the Netherlands) or a 1.5 Teslar (Vision-Siemens, Erlangen, Germany) scanner. Short TR/TE (T1-weighted images) as well as long TR/TE (T2-weighted), and fat suppressed (STIR, T2 Spir) sequences were evaluated. Using high intensity T1- and T2-weighted images, replacement of fatty bone marrow by marrow edema (low signal intensity in T1-, high signal intensity in T2-images) was observed. None of the MRI

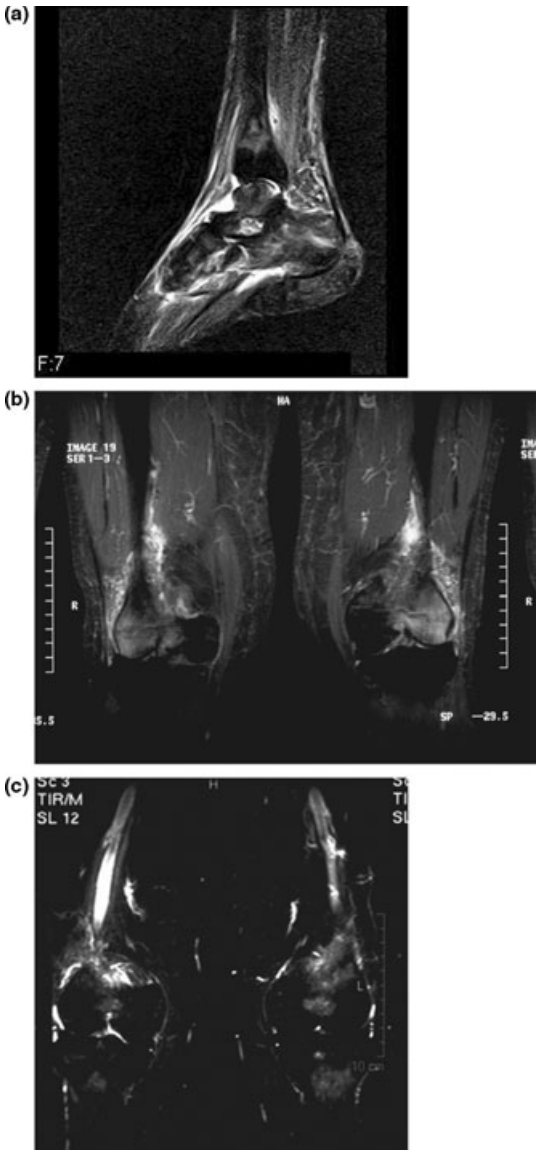

Figure 1a–c Typical clinical course of a 44 year old female patient with PTDLS: Osteoedema of the tarsal bones 3 months post-transplantation (top). Bilateral osteoedema of the femur condyles 7 months post-transplantation (middle). Osteoedema of the femur condyles 12 months post-transplantation (bottom). Notice the typical bilateral manifestation. Total duration of clinical symptoms: 16 months. Maximal AP elevation: 718 U/l.

scans revealed features indicative of osteonecrosis, which led to classification as stage ARCO-I (Association Research Circulation Osseous) in all cases. All alterations of the bone marrow were restricted to the lower distal limbs with involvement of the weight bearing structures of the knees and or feet. In the 37 patients, a total of 66 MRIs were performed. Of note, plain film radiographs did not show any abnormalities except a slight osteoporosis in nine patients.

Immunosuppressive protocol

Most of the patients had no complications after renal transplantation with spontaneous graft function in 27 patients (73%). Six patients (16.2%) required steroid pulse therapy following renal transplantation. Delayed graft function defined by the requirement of hemodialysis was observed in 10 out of 37 patients (27%). All patients were on a CNI-based immunosuppressive protocol (30 on cyclosporine, seven on tacrolimus); however, a specific risk for the use of cyclosporine versus tacrolimus could not be concluded from our data. The use of mycephenolat-mofetil (MMF) as part of a triple drug immunosuppressive protocol is standard at our institution within the first year after renal transplantation, we therefore cannot draw conclusions from the fact that all patients with PTDLS were on MMF at the start of symptoms. Major transplant characteristics of the patient cohort were compared with a cohort of renal transplant recipients without the syndrome (Table 1), showing no major differences in the immunosuppressive drug regimens and the cumulative steroid dosage.

Statistical analysis

Values are expressed as mean ± standard deviation of the mean and range. Statistical significance was tested using the Wilcoxon rank-sum test. A *P*-value of 0.05 or less was considered significant.

Results

Anatomic location of bone marrow edema

Osteoedema was located in the knees in 17 patients, in the feet in 11 patients and in both knees and feet in nine patients. Additional joint effusions were detected in nine out of 37 patients (24.3%). The development of osteoedema in every patient was proven by MRI-scans.

Laboratory findings

Alkaline phosphatase (AP) levels were within normal limits on the day of transplantation (113 ± 65 U/l). All patients showed a statistically significant increase in levels of AP (measured at 25°C) with a mean maximum AP level of 338 ± 152 U/l (range 126–804 U/l). The mean difference between the AP levels measured directly before transplantation and at the time of first MRI-diagnosis of bone marrow edema was 159 ± 95 U/l (range 17–424). Remarkably, the AP level started to rise significantly 2 months before the onset of clinical symptoms and turned out to be a good early marker of the disease. The mean AP levels 3 months before onset of symptoms were 160 ± 54 U/l and rose to 271 ± 108 U/l at the time of initial symptoms ($P = 0.0001$). Thereafter, AP levels stayed elevated for 7.0 ± 4.4 months, exceeding the duration of symptoms by 1.9 months. Mean serum calcium levels also rose significantly over 3 months from 2.46 ± 0.18 mmol/l to 2.58 ± 0.18 at the onset of symptoms ($P = 0.013$). Elevation of serum calcium levels lasted much shorter than the elevation of AP levels (Table 2). Clinical signs of hypercalcemia were not reported in any patient. Levels of parathyroid hormone did not seem to

Table 1. Comparison of transplant characteristics between renal transplant recipients with PTDLS and a control group without the syndrome. The control group was matched for age, creatinine, organ source, time of blood measurements after renal transplantation. All patients of the PTDLS and control group were on a CNI-based immunosuppressive protocol.

	PTDLS group ($n = 37$)	Control group ($n = 37$)	*P*-value
Age (years)	50.4 ± 10.9	50.3 ± 15.5	n.s (matched)
Creatinine (mg/dl)	1.59 ± 0.40	1.73 ± 0.72	n.s (matched)
Organ source (cadaveric versus living)	28/9	28/9	n.s (matched)
Time point of blood measurements after NTx (months)	5.8 ± 4.8	5.2 ± 2.0	n.s (matched)
CsA trough level (ng/ml)	147 ± 26 ($n = 30$)	136 ± 32 ($n = 26$)	n.s
FK trough level (ng/ml)	8.8 ± 1.7 ($n = 7$)	8.6 ± 3.1 ($n = 11$)	n.s
Steriod rejection therapies per patient	0.16 ± 0.37	0.11 ± 0.32	n.s
Prednisolon dosage (mg/day)	6.0 ± 1.8	5.8 ± 1.8	n.s
Alkaline phosphatase levels (U/l)	271 ± 108	173 ± 75	$P = 0.001$
Intact PTH levels (pmol/l)	13.9 ± 10.7	17.1 ± 10.6	n.s

Table 2. Calcium and alkaline phosphatase (AP) levels in 37 patients with PTDLS 3 months before to 9 months after start of bone pain.

	−3	−2	−1	0	+6	+9
Calcium (mmol/l)	2.46 ± 0.18	2.46 ± 0.16	2.55 ± 0.18	2.58 ± 0.18	2.40 ± 0.16	2.50 ± 0.17
P-value	–	0.421	0.038	0.013	0.490	0.300
AP (U/l)	160 ± 54	199 ± 59	229 ± 83	271 ± 108	298 ± 132	306 ± 134
P-value	–	<0.001	<0.000	<0.000	<0.000	0.004

0 = start of symptoms, values are expressed as mean ± SD, statistical analysis calculations used −3 (3 months before onset of bone pain) as reference level.

be a risk factor for PTDLS. PTH was measured using the intact PTH-assay Fa (Roche Diagnostics, Rotkreuz, Switzerland). Of the 37 patients, 27 had PTH levels lower than 15 pmol/l at the time of diagnosis of PTDLS, six between 15 and 29 pmol/l and four between 30 and 59 pmol/l. Higher PTH levels were not documented, showing that there was no evidence of concomitant severe hyperparathyroidism. Compared to a control group without the syndrome mean PTH levels were not different in osteoedema patients (Table 1). Liver function tests were uniformly normal in osteoedema patients and controls, indicating the absence of CNI-induced hepatotoxicity as a potential source of elevated AP levels.

Therapeutic trials

Initially, patients were given the advice to refrain form physical activity to reduce motion induced pain. Of the 37 patients, 22 had already received CCB at the time of diagnosis, a drug class that was supposed to be at least protective with regard to the development of PTDLS. At the time of diagnosis of PTDLS, 18 out of our patients had already received amlodipine, one patient lercanidipine, two patients nitrendipine, and one patient a retarded form of nifedipine. A new prescription of nifedipine 10 mg tid in one patient did not result in pain alleviation. Two patients were treated with hyperbaric oxygen as a therapeutic trial with no positive effect. This therapy was abandoned when the second patient experienced hyperbaric ear trauma. A change of the immunosuppressive regimen from cyclosporine to tacrolimus in four patients was not successful either. One patient developed osteoedema of the knees while under cyclosporine and, after a symptom free interval, in the feet after conversion to tacrolimus. No patient was switched to a CNI-free immunosuppression to avoid risk of graft rejection.

Long term outcome

For long term follow-up only 35 patients were eligible as two patients were lost to follow up evaluation. Although severe bone pain was noted in our patients, long term sequelae were not observed. After a mean follow-up period of 51.6 ± 28.6 months, no patient developed persisting functional impairment of cartilage or bone structures within the affected joints or premature osteoarthritis. Joint effusions were also of transient nature. A transition from bone marrow edema to overt osteonecrosis did not occur in any patient. Remarkably, recurrence of bone marrow edema was noticed in two patients after a symptom-free interval. These two patients are currently free of symptoms and without long-term sequelae either. Renal function remained stable over the time course. Mean creatinine at the last follow-up in the remaining 35 patients was 1.79 ± 0.68 mg/dl (range 0.80–4.40) representing an eGFR of 42.0 ± 16.1 ml/min (range 11.3–81.2) using the modified MDRD equation. There were no statistically significant differences in renal function comparing creatinine values ($P = 0.15$) or eGFR ($P = 0.28$) at diagnosis of PTDLS and on long-term follow up 51 months later, respectively.

Discussion

Bone disease is common after renal transplantation leading to a fracture rate of about 3% per year, osteonecrosis of the hip or immobilizing bone pain of the distal limbs [2]. A postoperative rise in AP levels with the use of cyclosporine in contrast to a regimen of azathioprin/steroids has been known from the early use of cyclosporine in the field of renal transplantation [15–17]. Obviously, on one hand, the high prevalence of pre-existing bone disease due to renal hyperparathyroidism [18–20], concomitant diabetes mellitus [21,22], severe atherosclerosis or acidosis [23], and numerous other different conditions, contributes significantly to post-transplant bone disease. On the other hand, numerous other factors associated with renal transplantation itself, including immobilization [24], use of steroids [25], persistent renal hyperparathyroidism [26], renal phosphate wasting [27], uremia and malnutrition [23] may also lead to bone loss and osteopenia, thus favouring the clinical manifestation of bone disease. The role of cyclosporine and tacrolimus in bone remodelling after

transplantation is still discussed controversially. *In vivo* animal models demonstrated high-turnover bone disease associated with these immunosuppressive agents [28–30]. A positive correlation of cyclosporine blood concentrations with AP levels related to increased osteoblast and osteoclast activation has also been reported [31]. However, other studies did not confirm major deleterious effects of calcineurin-inhibitors on bone metabolism [32,33].

Post-transplant distal limb syndrome seems to differ significantly from all of the above mentioned mechanisms of post-transplant bone disease in its unique clinical, laboratory and long term presentation. All patients reported uniformly a 'waxy', wandering (from left to right and vice versa), and over time, waning pain syndrome of the knees and or ankles and feet, with different weight-bearing bone regions affected on physical stress. The pain was described as being dull and alleviated on rest. Consistent with pain relief on rest, we assume physical exercise in conjunction with individual vulnerability, to play a partial role for this peculiar presentation. The overall benign clinical course on long-term follow up and the unremarkable physical examination were inconsistent with the diagnosis of reflex dystrophy syndrome as suggested by Muno-Gomez and colleagues [34]. Serial MRI scans in some patients revealed that the most painful bone regions, as pointed out by the patients, showed the largest areas of bone marrow edema. Some patients experienced sympathetic joint effusions. These effusions were transient in nature and were not punctured routinely.

In our patients, laboratory analysis revealed a statistically significant increase in AP levels concomitant or even prior to the onset of clinical symptoms. A concomitant rise in serum calcium levels was also noticed. Therefore, a rise in serum AP levels and to a lesser extent in serum calcium levels in renal transplant patients may serve as early indicators of PTDLS. In this setting, further MRI evaluation in patients with distal lower limb pain should be considered to prove the syndrome and exclude steroid-induced osteonecrosis.

All patients were treated on a CNI-based standard immunosuppressive regimen with cyclosporine or tacrolimus, indicating the possible etiologic role of calcineurin-inhibitors in PTDLS. Nevertheless, we did not find a positive association of the syndrome with CNI-trough levels in our patients, supporting the controversial role of CNI on bone remodelling as described above. Mean cyclosporine and tacrolimus trough levels were within expected limits. Switching from cyclosporine to tacrolimus in four patients did not result in any improvement in clinical symptoms. Compared with a control group without the syndrome, CNI-trough levels were not higher in osteoedema patients but well within expected levels of maintenance immunosuppression (Table 1).

In contrast to earlier reports, CCB did not have a protective effect in our patients. 22 out of 37 patients had already been treated with CCB at the time of MRI diagnosis of PTDLS. We therefore conclude that CCB are at least not protective with regard to the development of bone marrow edema as suggested by Gauthier *et al.* [14].

The cumulative steroid-dose in our patients was within expected limits, as was the number of steroid pulses for rejection therapy. Therefore, we feel that steroids do not play a major role in the pathogenesis of PTDLS. Noteworthy, one of our patients did not receive any steroid medication at all at the time of diagnosis. In line with this finding are reports of distal lower limb pain in solid organ recipients other than renal transplants (combined kidney-pancreas, liver, lung) on a CNI-based immunosuppressive protocol [14], suggesting that parathyroid hormone levels as well as duration of ESRD and stage of kidney function do not play a major contributory role. In keeping with these reports, PTH levels were low in our osteoedema patients and did not differ from PTH levels of the controls (Table 1).

Surprisingly, two of our patients experienced a second episode of PTDLS after a symptom-free interval with again complete resolution over the time. A definite cause of the second presentation could not be elucidated either. Nevertheless, these patients were still on a CNI-based immunosuppressive protocol during the second episode.

To the best of our knowledge, this study represents the largest cohort of patients with MRI-proven PTDLS. Furthermore, we provide long term follow up data on kidney function and bone outcome. Mean kidney function measured via eGFR using the modified MDRD-formula was good at the time of diagnosis and remained remarkably stable during follow up over 51 months. Why this syndrome, at least in our cohort, mainly affected kidney transplant recipients with a comparable favourable clinical course and overall good graft function, and why so far no clear significant correlation with CNI-trough levels could be found, remain unclear and might be the subject of further research. As the development of painful bone marrow edema on MRI-scans is also common in other diseases not related to transplantation or use of specific medication [35], bone marrow edema might emerge because of a common final pathway of disturbed bone microcirculation and or metabolism. Nevertheless, non-transplant related causes of bone marrow edema in our cohort were tried to rule out via thorough medical chart reviewing. So far, the etiology of the syndrome is still controversially discussed [36]. Of further note is the fact that bone pain syndromes caused by bone marrow edema related to cyclosporine medication have also been described in clinical settings different from transplantation

[37], thus raising the probability of CNI-medication as at least one major etiologic agent in the development of the syndrome. As the syndrome displays a benign and time-limited course in patients with an acceptable graft function on long-term follow up, we would only cautiously suggest conversion to a less immunosuppressive protocol. Up to now, no other factor predisposing to PTDLS than medication with CNIs has been definitely identified. Thus, further prospective studies are clearly necessary to unravel the pathophysiologic mechanism and elucidate further potential risk factors of PTDLS.

Limitations to the study

As a retrospective observational study, there are several limitations. First, although PTDLS is a rare syndrome the low patient number did not allow further evaluation of potential risk factors with regard to the development of this entity. Two patients were lost to follow-up thus reducing patient numbers even further. We tried to rule out other potential causes of osteoedema in our patients through medical chart reviewing (trauma, anorexia and different forms of malnutrition, coagulation disorders, sickle cell anemia, alcoholism and heavy cigarette smoking e.g.). Because of the retrospective nature of our study, there might thus be some unaccounted bias in this effort. Nevertheless, we feel that the information provided might be useful in further studying this rare and presumably often overlooked complication following solid organ transplantation in patients on a CNI-based immunosuppressive protocol.

Conclusion

PTDLS typically develops within 1 year after solid organ transplantation. It differs from steroid induced aseptic osteonecrosis in terms of anatomic location, an average cumulative steroid dose and a benign long-term bone outcome. Nevertheless, it might lead to significant morbidity because of immobilization. PTDLS seems to be associated with a rise in AP as an early laboratory indicator of the syndrome. Thus, we recommend early MRI evaluation in transplant patients with bone pain of the knees and/or feet and a concomitant rise in AP levels to rule out osteonecrosis and to diagnose PTDLS definitely.

Authorship

F-PT: performed the study, collected data, analyzed data, wrote paper. MJ: collected data. DB: collected data. MO: collected data. L-CR: designed the study. BG: designed the study. G-RH: analyzed data, wrote the paper.

References

1. Parfrey PS, Fargo D, Parfrey NA, *et al.* The decreased incidence of aseptic necrosis in renal transplant recipients: A case control study. *Transplantation* 1986; **41**: 182.
2. Heaf JG. Bone disease after renal transplantation. *Transplantation* 2003; **75**: 315.
3. Wiliams PS, Hillis AN, Carty AJ, *et al.* Symptomatic renal osteodystrophy after renal transplantation: Treatment with 1-alpha-hydroxycholecalciferol. *Transplant Proc* 1987; **19**: 2227.
4. Coates PTH, Tie M, Russ GR, *et al.* Transient bone marrow edema in renal transplantation: A distinct post-transplantation syndrome with a characteristic MRI appearance. *Am J Transplant* 2002; **2**: 467.
5. Stevens MS, Hilson AJW, Sweny P. Post-renal transplant distal limb bone pain. *Transplantation* 1995; **15**: 305.
6. Torregrosa JV, Campistol JM. Reflex sympathetic dystrophy syndrome in renal transplant patients: A mysterious and misdiagnosed entity. *Nephrol Dial Transplant* 1999; **14**: 1364.
7. Collini A, De Bartolomeis C, Barni R, *et al.* Calcineurin-Inhibitor induced pain syndrome after organ transplantation. *Kidney Int* 2006; **70**: 1367.
8. Hetzel GR, Malms J, May P, *et al.* Post-transplant distal-limb bone marrow oedema: MR imaging and therapeutic considerations. *Nephrol Dial Tranplant* 2000; **15**: 1859.
9. Lucas VP, Ponge TD, Plougastel-Lucas ML, *et al.* Musculoskeletal pain in renal-transplant recipients. *N Engl J Med* 1991; **325**: 1449.
10. Goffin E, Vande Berg B, Devogelaer JP, *et al.* Post-renal transplant syndrome of transient lower limb joint pain: Description under a tacrolimus-based immunosuppression. *Clin Nephrol* 2003; **59**: 98.
11. Goffin EJ. Calcineurin-inhibitors and bone pain after organ transplantation. *Kidney Int* 2007; **71**: 468.
12. Eustace S, Keogh C, Blake M, *et al.* MR imaging of bone oedema: Mechanism and interpretation. *Clin Radiol* 2001; **56**: 4.
13. Puig I, Mari JM, Martinez-Miralles E, *et al.* Reflex sympathetic dystrophy syndrome of the lower limbs in a renal transplant patient treated with Tacrolimus. *Transplantation* 2000; **70**: 210.
14. Gauthier VJ, Barbosa LM. Bone pain in transplant recipients responsive to calcium channel blockers. *Ann Intern Med* 1994; **121**: 863.
15. Rambausek M, Ritz E, Pommer S, *et al.* Alkaline phosphates levels in renal transplant recipients receiving cyclosporine or azathioprin/steroids (letter to the editor). *Lancet* 1988; **1**: 247.
16. Kahan BD. Cyclosporine. *N Engl J Med* 1989; **321**: 1725.
17. Kahan BD, Flechner SM, Lorber MI, *et al.* Complications of cyclosporine-prednisone immunosuppression in 402 renal allograft recipients exclusively followed at a single

center for from one to five years. *Transplantation* 1987; **43**: 197.
18. Atsumi K, Kushida K, Yamaszaki K, *et al.* Risk factors for vertebral fractures in renal osteodystrophy. *Am J Kidney Dis* 1999; **33**: 287.
19. Taal MW, Masud T, Green D, *et al.* Risk factors for reduced bone density in hemodialysis patients. *Nephrol Dial Transplant* 1999; **14**: 1922.
20. Bianci ML, Colantonio G, Montesano A, *et al.* Bone mass status in different degrees of chronic renal failure. *Bone* 1992; **13**: 225.
21. Levin ME, Boisseau VC, Avioli LV. Effects of diabetes-mellitus on bone mass in juveniles and adult-onset diabetes. *N Engl J Med* 1976; **294**: 241.
22. Munos-Torres M, Jodar E, Escobar-Jimenez F, *et al.* Bone mineral density measured by dual X-ray absorptiometry in Spanish patients with insulin-dependent diabetes mellitus. *Calcif Tissue Int* 1996; **58**: 316.
23. Heaf JG, Tvedegaard E, Kanstrup IL, *et al.* Bone loss after renal transplantation: Role of hyperparathyroidism, acidosis, cyclosporine and systemic disease. *Clin Transplant* 2000; **14**: 457.
24. Kwan JTC, Almond MK, Evans K, *et al.* Changes in total body bone mineral content and regional bone mineral density in renal patients following renal transplantation. *Miner Electrolyte Metab* 1992; **18**: 166.
25. Canalis E. Mechanisms of glucocorticoid action on bone. *Curr Osteoporos Rep* 1996; **3**: 98.
26. 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.
27. Pabico RC, McKenna BA. Metabolic problems in renal transplant patients. *Transplant Proc* 1988; **1**(Suppl 1): 438.
28. Stein B, Takizawa M, Katz I, *et al.* Salmon calcitonin prevents cyclosporine-A-induced high turnover bone loss. *Endocrinology* 1991; **129**: 92.
29. Cvetkovic M, Mann GN, Romero DF, *et al.* The deleterious effects of long-term cyclosporine A, cyclosporine G and FK506 on bone mineral metabolism in vivo. *Transplantation* 1994; **57**: 1231.
30. 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.
31. Briner VA, Landmann J, Brunner FP, *et al.* Cyclosporin A induced transient rise in plasma alkaline phosphatase in kidney transplant patients. *Transpl Int* 1993; **6**: 99.
32. Grotz W, Mundinger A, Gugel B, *et al.* Missing impact of cyclosporine on osteoporosis in renal transplant recipients. *Transplant Proc* 1994; **26**: 2652.
33. Dumoulin G, Hory B, Nguyen NU, *et al.* Lack of evidence that cyclosporine treatment impairs calcium-phosphorus homeostasis and bone remodelling in normocalcemic long-term renal transplant recipients. *Transplantation* 1995; **59**: 1690.
34. Muno-Gomez J, Collado A, Gratacos J, *et al.* Reflex sympathetic dystrophy syndrome of the lower limbs in renal transplant patients treated with cyclosporine A. *Arthritis Rheum* 1991; **34**: 625.
35. Van de Berg BC, Malghem J, Lecouvet FE, *et al.* Distribution of serouslike bone marrow changes in the lower limbs of patients with anorexia nervosa: Predominant involvement of the distal extremeties. *Am J Rheum* 1996; **166**: 621.
36. Goffin E. Transient bone marrow edema in renal transplantation: A distinct post-transplantation syndrome with a characteristic MRI appearance. *Am J Transplant* 2003; **3**: 96.
37. Isaacs KL. Severe bone pain as an adverse effect of cyclosporin therapy for Crohn's disease. *Inflamm Bowel Dis* 1998; **4**: 95.

