Invited Comment

Bone disease after renal transplantation

Heide Sperschneider and Günter Stein

Department of Internal Medicine IV, Friedrich-Schiller-University, Jena, Germany

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Introduction

Kidney transplantation largely restores defective exocrine and endocrine renal function in patients with end-stage renal disease (ESRD). This in turn is expected to lead to a progressive correction of established renal bone disease. This widely held assumption, however, lacks convincing evidence from experimental and clinical data published thus far. A major obstacle to the investigation of renal osteodystrophy in transplant recipients has been its unpredictable evolution under the multiple biochemical and hormonal influences that regulate mineral metabolism and bone turnover independently. The clinical and histological features of the pre-existing uraemic bone disease at the time of kidney transplantation are highly variable. Moreover, its course after transplantation depends on persisting abnormalities such as hypercalcaemia, hypophosphataemia and hypomagnesaemia as well as on the type, dose and duration of immunosuppressive medications that are needed to minimize allograft rejection. These factors operate additively and their effects are often difficult to dissociate from the already existing osteopathy.

The existence and type of post-transplant bone disease may not be recognized correctly and appropriate therapy may not be started in time. Although glucocorticoid therapy represents a pathogenetic key factor other immunosuppressive drugs such as cyclosporine, tacrolimus, azathioprine and rapamycin clearly contribute to its prevalence and expression through their pleiotropic pharmacological effects. These drugs have been shown to increase overall bone turnover and/or to stimulate loss of bone mass independently. Based on currently available data, only mycophenolate mofetil appears to have a neutral effect in this regard [1].

Only a limited number of reports dealt with this problem in the past. There is an obvious need for well-designed prospective studies with sufficient patient numbers to determine the relative importance of the numerous factors involved in the perturbed bone remodelling following kidney transplantation. Furthermore, a consensus-based classification of the various types of renal allograft-associated osteopathy, including clinical, radiological and histomorphological criteria, might lead to a more reliable basis for experimental research into this particular disease and facilitate the comparison between studies. When working up a patient for symptoms and signs of renal transplant-associated bone disease, clinical data for an effective evaluation and treatment of this condition are often lacking. A longitudinal analysis of the disease process would undoubtedly allow a more precise diagnosis and a more appropriate care of post-transplant bone disease. In many cases, follow-up data from the time of transplantation or before are unavailable or inaccessible. Radiographic examinations of the thoracic and lumbar spine with a bone densitometry of the femoral neck or other sites, and an iliac crest biopsy with a histomorphometric analysis in at least some patients should be ideally obtained before a diagnosis is made and a treatment is initiated. Several main osteological complications of kidney transplantation will be reviewed in the following, as summarized in Table 1.

Persistent secondary hyperparathyroidism (HPT)

The diagnosis of persistent secondary HPT is rarely based on histomorphological data, but only on elevated serum immunoreactive parathyroid hormone (iPTH) levels. Increased serum iPTH concentrations are regularly found until 6 months after renal transplantation. After 1 year, iPTH values greater than twice the normal limit are still present in more than 50% of patients, and after 2 years in ~27% of patients [2,3]. Persistently high serum iPTH levels have been attributed to a relatively slow decrease of an oversized total parathyroid gland mass [4], in particular in

Correspondence and offprint requests to: Prof. Dr Heide Sperschneider, KfH Kuratorium für Dialyse und Nierentransplantation e. V., Zur Lämmerlaide 1, D-07751 Jena-Drackendorf, Germany. Email: heide.sperschneider@kfh-dialyse.de

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association with monoclonal, autonomous parathyroid tissue growth.

Persistent HPT is a known risk factor for increased bone turnover and decreased overall bone density. Patients with serum iPTH levels > 25 pmol/l prior to renal transplantation have the highest rate of bone loss post-transplant and are at increased risk for a delayed recovery of renal transplant function [5]. Most studies documented an increased bone turnover during the first 5–6 months after transplantation based on serum biochemistry, characterized by an increase in serum iPTH, alkaline phosphatases and osteocalcin. Since PTH tonically stimulates osteoblast function this may result in an apparent normalcy of serum markers of active bone formation, although there may be a decrease in total osteoblast reserve. The repeatedly observed inverse relation between serum 25(OH)D3 and iPTH points to a disturbed feedback regulation between these two factors although serum 1,25(OH)2D3 generally remains within normal limits. Pre-existing histological bone abnormalities usually fail to resolve within 2 years after renal transplantation [6].

Recent studies suggest that serum iPTH alone may not be a valid marker of bone turnover in renal transplant recipients. Other serum markers of bone metabolism should be determined as well [6–10]. This leads to the question whether we possibly overestimate serum iPTH when monitoring kidney transplant recipients, and which cut-off value should be used to define secondary HPT in this condition. Torres et al. [3], who performed a meta-analysis of several reports with determinations of serum iPTH levels at various time intervals after kidney transplantation [8–11], surprisingly noticed elevated iPTH concentrations in the presence of high and also of low bone turnover (i.e. respectively, osteitis fibrosa and adynamic bone disease). To make things even more complicated, low turnover osteopathy may go along with either preserved or defective bone mineralization, depending on bone receptor density and or the presence or absence of steroid medication [9,11]. The main risk factors for persistent HPT in renal transplant recipients are long-term pre-transplant dialysis treatment and an increase in pre-transplant serum iPTH levels to more than three times the upper limit of normal.

These observations suggest that in renal patients with secondary HPT, who are on a transplantation waiting list, the medical treatment of parathyroid overfunction should be intensified, and surgery should be considered timely for those resistant to medical treatment. The estimated frequency of parathyroidectomy following renal transplantation is currently ~ 5%. However, this type of surgery has its own risks, including a possible deterioration of graft function in up to 20% of the patients owing to chronic hypercalcaemia. The possible value of calcimimetic agents to prevent this problem is unclear at present [12].

Finally, hypophosphataemia is a frequent problem after kidney transplantation. It is observed in ~ 90% of graft recipients for the first 4 months and in 20–40% at 1 year. Its pathogenesis is complex, and it is often associated with subnormal graft function. Moreover, it may promote osteomalacia. In clinical practice, oral phosphate supplementation is often maintained beyond actual needs and at unnecessarily high doses. Such overtreatment can even induce secondary HPT [13–15].

### Post-transplant osteoporosis

Rapid loss of bone mass has been reported in 28–88% of graft recipients after renal transplantation. The loss may be extensive, at an estimated rate of 6.8% during the first year after transplantation [16–21]. The rate at which bone mass is lost gradually decreases with time, with a residual annual rate of 1.7% being found by the 10th year after renal transplantation based on bone histology with a large prevalence of osteoporosis. This condition arises from an overall decrease in bone mineralization together with a reduction in bone formation. Long-term glucocorticoid administration and possibly cyclosporine treatment may chronically activate osteoclasts in spongy and/or cortical bone while osteoblast activity is inhibited. This in general goes along with a low bone turnover state. As a consequence, up to 40% of renal graft recipients have spontaneous osteoporotic pain. The highest incidence of bone fractures occurs at ~2 years post-transplant. Approximately 22% of the patients will experience fractures at least once during follow-up, with an absolute risk three times that of age-matched controls [19,22]. From a clinical point of view, two caveats are important to consider when osteodensitometry findings are evaluated in patients with suspected post-transplant osteoporosis. (i) Pre-existing abnormalities such as renal osteodystrophy, extra-osseous calcifications and mechanical bone deformation owing to hypophosphataemic osteomalacia may significantly bias the diagnostic power and preclude any specific conclusion in the absence of a longitudinal follow-up. Furthermore, since osteoporosis is frequent in post-menopausal patients, it may be indistinguishable from post-transplant osteoporosis based on radiographic criteria [23]. (ii) When interpreting radiographic studies, it should be borne in mind that osteoporosis
in renal transplant recipients is usually associated with high bone turnover and an increase in serum levels of various markers of bone metabolism.

Several circulating markers such as tartrate-inhibitable alkaline phosphatase 5b (TRAP 5b), pyridinium cross-laps or cross-linked telopeptide have been shown to correlate with osteoclast activity. However, their clinical value for the diagnosis of low bone remodelling is as yet unproven. These markers are acceptable clinical parameters for the evaluation of the effectiveness of anti-resorptive therapies, although their usefulness as predictors of fracture risk in place of radiographic scores still remains to be determined.

Steroid medication is a well known risk factor for osteoporosis and there is no known threshold dose. In clinical practice, some patients fail to benefit from daily doses as low as 2.5–7.5 mg of prednisone, whereas daily doses > 7.5 mg will definitively induce osteoporosis in the majority of patients. An inverse relation between cumulative steroid dose and decreased bone mass has been demonstrated by Monier-Faugere et al. [9]. Furthermore, vitamin D receptor polymorphism may play a role [24].

Considering cyclosporine, solely experimental animal data suggest an independent pathogenetic role in post-transplant osteoporosis [1].

In the absence of established clinical data, current guidelines for the prevention and treatment of osteoporosis in renal transplant recipients mainly rely on published evidence from other forms of osteoporosis. The following preventive measures have been suggested to reduce the risk of fractures: (i) use of low corticosteroid doses for a limited time period in the pre-transplant period in patients with ESRD waiting for transplantation; (ii) 30 min of vigorous physical exercise or daily physiotherapy; (iii) identification and treatment of risk factors for osteoporosis; (iv) no alcohol or nicotine consumption; and (v) hormone replacement therapy in post-menopausal women.

Specific drug treatment includes supplementation of calcium via calcium carbonate and prescription of anti-resorptive drugs, e.g. vitamin D metabolites, bisphosphonates, calcitonin and/or oestrogens depending on the clinical picture. Thus, repeated intravenous administration of 0.5 mg/kg pamidronate immediately after transplantation and 4 weeks later led to a significant reduction in bone loss at the femoral neck and lumbar vertebrae over a period of 12 months [25]. In patients with a bone density T-score > 2.5 and in those with a history of bone fractures, diabetes mellitus or a combined kidney/pancreas transplantation, a treatment with bisphosphonate, vitamin D 3, and/or calcium supplementation is strongly recommended [21,26].

The administration of low doses of active vitamin D derivatives and calcium has been shown to prevent partial bone loss at the lumbar spine and proximal femur when given for the first 6 months after transplantation. Bisphosphonates may also be symptomatically useful, by reducing osteoporotic bone pain [27]. Finally, recombinant PTH administration may be indicated in the future [28,29].

Pain in the distal extremities ['symmetric bone pain syndrome'; ‘calcineurin inhibitor-induced pain syndrome’ (CIPS)]

Primary musculoskeletal pain has been reported in 19–35% of renal transplant recipients [30–32]. The syndrome is characterized by symmetrical resting pain in the legs [30,33]. More than 10% of patients receiving cyclosporine therapy for kidney transplantation will experience spontaneous symmetrical musculoskeletal pain of no obvious other origin [30]. The syndrome is at present recognized as an independent entity and may be difficult to differentiate from musculoskeletal pain secondary to HPT, sensory polyneuropathy, gout, osteoporosis or avascular bone necrosis. The diagnosis therefore is largely one by exclusion. Its pathogenesis remains unclear. Microscopic epiphyseal fractures with marrow oedema, localized micro-vascularitis and ill-defined alterations of the pain threshold have all been implicated. Magnetic resonance imaging (MRI) and bone scintigraphy may help identify areas of localized inflammation to establish the diagnosis. In the case of cyclosporine-associated pain, FK-506 may be used instead [30,32,33]. Finally, calcitonin may be useful to treat skeletal pain. Alternatively, calcium-channel antagonists, active vitamin D derivatives, and short-term administration of non-steroidal anti-inflammatory drugs may be worthwhile.

Spontaneous femoral head necrosis/localized osteonecrosis

The prevalence of spontaneous osteonecrosis of the femoral head has declined in the past from 15 to 4.8% at present. The main risk factor remains chronic corticosteroid administration [34,35]. Localized vascularitis of the bone, vascular thrombosis and fatty embolism have been shown to cause osteonecrotic lesions. Conventional X-ray or better MRI will allow the diagnosis in most cases. The condition is usually treated by early surgical decompression of the femoral head to prevent venous congestion or endoprosthetic replacement. Calcitriol treatment has been shown to normalize bone metabolism, to decrease bone loss and to substantially reduce the risk of femoral head necrosis in kidney transplant patients [34].

\( \beta_2 \) Microglobulin (\( \beta_{2M} \)) amyloidosis

The recovery of normal renal function in renal graft recipients leads to the regression of \( \beta_{2M} \)-associated disturbances of bone metabolism. Articular \( \beta_{2M} \) deposits are frequently present and may remain detectable 10 years after transplantation [39]. \( \beta_{2M} \) amyloidosis may promote local inflammation and thereby favour chronic destructive arthropathy. Therefore, symptomatic patients with localized bone pain and no other diagnosis should be additionally screened for \( \beta_{2M} \) amyloidosis.
using X-ray, MRI, bone scintigraphy, or a biopsy. Fortunately, in the majority of patients the clinical expression of β2M amyloidosis decreases or even disappears after renal transplantation [36].

Conclusion

The persistently high prevalence of post-transplantation osteopathies, particularly of HPT and osteoporosis, should prompt us to place greater and more rigorous emphasis on active diagnostic and therapeutic measures to minimize treatable risk factors. Ideally, the careful monitoring of each patient’s clinical course should start long ahead of renal transplantation, with target serum iPTH levels being meticulously kept at two to three times the upper limit of normal by adequate medical or surgical therapy. The use of non-steroidal immunosuppressants or low-dose corticosteroid regimens to prevent allograft rejection in combination with prophylactic anti-resorptive bone therapy at the time of transplantation will help to avoid an accelerated loss of bone mass with age in renal transplant patients. Future research will need to focus on these aspects.

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