The Bone after Kidney Transplantation

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At the time that a patient with CKD receives a kidney graft, his or her bone structure is generally not normal. The bone has undergone more or less marked changes during the course of CKD before transplantation. Both the type and the severity of renal osteodystrophy (that is, one of the three main components of CKD-associated bone disorder) depend on numerous factors, including underlying cause of CKD, type and severity of metabolic disturbances, duration of CKD, presence of diabetes, gonadal dysfunction, concomitant age, sex- and ethnicity-related skeletal changes, modality of kidney replacement therapy, and medications received (1). High-turnover bone disease, which is essentially the histologic expression of secondary hyperparathyroidism, has long been the predominant type of renal osteodystrophy. In the last two decades, low-turnover bone disease, mostly of the adynamic type, has become increasingly prominent in patients on dialysis (2).

Initial bone mass and bone quality may differ markedly from one kidney graft recipient to another. Ideally, one would like to know what the effects are of a successful transplantation per se on the bone and the roles of baseline renal osteodystrophy, persistent secondary hyperparathyroidism and gonadal dysfunction, and immunosuppressive agents. Most importantly, from the patient’s point of view, does kidney transplantation improve the high fracture risk associated with ESKD?

Numerous studies evaluated bone health by dual-energy x-ray absorptiometry (DXA) or more precise imaging techniques, such as high-resolution peripheral quantitative computed tomography. The majority of older studies showed a decrease in bone mineral density (BMD) 1 year or more after kidney transplantation, often exceeding 5%, and more specifically, they showed significant deterioration of both cortical and trabecular bone microstructure. In contrast, more recent studies reported either moderate or no BMD losses in the first year after transplantation, mainly at the peripheral skeleton but not the central skeleton (3,4), with stabilization or even slight recovery in subsequent years (3).

The fracture risk of transplant recipients is several-fold higher than that of healthy people and even higher than that of patients on maintenance dialysis during the first 3 years after transplantation, but it decreases thereafter (5,6). The decrease in fracture rates observed in more recent studies might be explained by improved renal osteodystrophy management before and less cumulative corticosteroid exposure after kidney transplantation (3,5,7). The skeletal effects of the other immunosuppressive agents remain uncertain.

The gold standard for assessing bone health is (quantitative) histomorphometric analysis of a bone biopsy. By informing on bone turnover and mineralization, a bone biopsy may provide pathophysiologic insights and allow for targeted therapy. However, the performance of a bone biopsy remains an invasive procedure, and expertise in histomorphometry is vanishing. Consequently, bone biopsy studies in kidney transplant recipients are scanty and often hampered by sample size and/or cross-sectional design.

In this issue of the CJASN, Keronen et al. (8) report the results of a prospective cohort study in 27 kidney graft recipients who consented to a first bone biopsy while still receiving dialysis therapy and a second bone biopsy 2 years after transplantation from deceased donors. Median age at time of second biopsy was 50 years old, 81% were men, and 41% had diabetes. Median dialysis vintage was 15 months before the first biopsy. All kidney recipients received triple immunosuppressive therapy (i.e., myco- phenolate mofetil, a calcineurin inhibitor, and methylprednisolone). A daily oral dose of 1 mg/kg methylprednisolone was given for 3 weeks, and then, it was progressively tapered to 4 mg/d after 3–6 months. Initially, median daily doses of 1500 mg calcium carbonate, 0.4 µg alfalcacaldol, 2.1 µg paricalcitol, and 30 mg cinacalcet were given, and after 2 years, 500 mg, 0.4 µg, 0 µg, and 75 mg, respectively, were given. For the sake of comparison, another 13 study participants who failed to receive a kidney graft and remained on dialysis treatment for 2 years underwent repeat bone biopsies as well. Their median age at the time of second biopsy was 55 years old, and their median dialysis vintage was 55 months.

The main bone histomorphometry finding in the transplant recipients was that the proportion of those with high bone turnover declined from 63% at baseline to 19% 2 years after kidney transplantation, whereas the proportion of the patients with low bone turnover increased from 26% to 52%. More than one third of the patients who were transplanted had low trabecular bone volume at baseline, and there was little change after 2 years. Remarkably, femoral neck T scores decreased significantly, whereas lumbar spine

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T scores remained unchanged. The histomorphometric distribution of low bone volume did not differ between low- and high-bone turnover groups at baseline or follow-up. Disappointingly, BMD or T scores measured by DXA, circulating mineral metabolism, and bone turnover biomarkers did not correlate with the histomorphometric findings.

The main strength of the study by Keronen et al. (8) is its prospective design, with a first bone biopsy before kidney transplantation and a repeat biopsy with histomorphometric analysis after a 2-year interval. Main limitations are the acceptance of repeat bone biopsies by only 27 among the 37 transplant recipients with baseline biopsy, lack of analysis of cortical bone, and BMD assessment by DXA in only a subset of patients with kidney transplants and patients on dialysis, reducing statistical power.

How do the observations of Keronen et al. (8) in Finland compare with the two recent studies in kidney transplant recipients with >15 repeat bone histomorphometry assessments (1,9)? First, bone histomorphometry parameters at the time of transplantation differed between studies. Most strikingly, a high bone turnover was observed in >50% of patients enrolled in the study by Keronen et al. (8) and Marques et al. (9) but only 3% of the patients enrolled in the study by Evenepoel et al. (1). Probably, patient mix (such as age, ethnicity, dialysis vintage, and CKD-associated bone and mineral disorder therapy), differences in diagnostic criteria, and selection bias account for these differences. For example, in the study by Evenepoel et al. (1), patients were recruited blinded for parameters of mineral metabolism, whereas in the study by Marques et al. (9), patients with previous parathyroidectomy or adynamic bone disease were excluded. Second, all studies showed marked declines in bone turnover after transplantation. Reviewing the kinetics of the changes, it seems that the decline in bone resorption precedes the decline in bone formation and that changes are more pronounced in patients with high bone turnover at baseline. This pattern aligns with circulating bone turnover marker level versus time profiles as recently determined in 69 de novo kidney transplant recipients (3). Such a pattern somehow refutes the hypothesis that increased bone calcium efflux is the main culprit of post-transplant hypercalcemia, a common complication in kidney transplant recipients, especially during the second half of the first post-transplant year. The observation of a high prevalence of low bone turnover disease in patients with post-transplant hypercalcemia (1,8) also argues against a predominant skeletal implication. Third, at variance with the two previous studies (1,9), bone mineralization defects worsened after transplantation in the study by Keronen et al. (8). The risk factors and pathophysiologic mechanisms contributing to impaired mineralization remain to be defined. Fourth, trabecular bone volume consistently showed little change after transplantation in all prospective bone biopsy studies, most probably reflecting low glucocorticoid exposure (1). Prospective studies evaluating cortical bone in de novo kidney transplant recipients are even more limited, and so far, they have yielded conflicting results (4,9). Marques et al. (9), who assessed cortical thickness and porosity by histomorphometry and high-resolution peripheral quantitative computed tomography, failed to demonstrate significant changes.

What can we learn from the repeat bone biopsy studies? First, bone turnover declines after kidney transplantation, and the magnitude of the decline seems to depend on severity of renal osteodystrophy at baseline. Second, post-transplant bone loss is limited overall with present low-dose glucocorticoid immunosuppression regimens, although it still occurs in a subset of patients. The contribution of impaired bone quality to the overall fracture risk in kidney transplant recipients remains ill defined and requires further investigations. Third, the weak or absent correlations of BMD or serum biochemistry parameters with histomorphometric findings is of concern, because we mostly rely on less invasive assessment tools than a bone biopsy. Fourth, whether knowledge of bone histology changes after kidney transplantation will allow for identifying more efficacious means to reduce fracture risk in the future remains to be demonstrated. Fifth, bone biopsy studies in kidney transplant recipients so far are hampered by small sample size with inherent risks of type 2 statistical errors. This calls for a concerted action in which bone biopsy efforts are combined (10).

Disclosures
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