Individualized Therapy to Prevent Bone Mineral Density Loss after Kidney and Kidney-Pancreas Transplantation

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Background and objectives: Most patients who undergo kidney or kidney-pancreas transplantation have renal osteodystrophy, and immediately after transplantation bone mineral density (BMD) commonly falls. Together, these abnormalities predispose to an increased fracture incidence. Bisphosphonate or calcitriol therapy can preserve BMD after transplantation, but although bisphosphonates may be more effective, they pose potential risks for adynamic bone.

Design, setting, participants, & measurements: A total of 153 kidney (61%) and kidney-pancreas (39%) transplant recipients were allocated to bisphosphonate (62%) or calcitriol (38%) therapy using an algorithm that incorporated BMD, prevalent vertebral fracture, biomarkers of bone turnover, and risk factor assessment. Patients received cholecalciferol and calcium as appropriate and were followed for 12 mo.

Results: Patients who were treated with bisphosphonates had lower BMD at the lumbar spine and femoral neck and longer time on dialysis. Age and gender were similar between the groups. At 12 mo, bisphosphonate-treated patients had significant BMD increases at the lumber spine and femoral neck and a negative trend at the wrist. Patients who were allocated to calcitriol, who were assessed to have lower baseline fracture risk, had no significant change in BMD at any site. At 1 yr, mean levels of bone turnover marker and intact parathyroid hormone normalized in both groups. Incident fracture rates did not differ significantly.

Conclusions: With targeted treatment, BMD levels were stable or improved and bone turnover markers normalized. This algorithm provides a guide to targeting therapy after transplantation that avoids BMD loss and may reduce suppression of bone turnover.

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Patients who have stage 5 chronic kidney disease (CKD) or who are on dialysis have a high fracture risk. For example, hip fracture is reported to be 4.4 times that of the general population with 2.4-fold greater mortality (1). Surprising, except for patients with type 1 diabetes, levels of bone mineral density (BMD) adjusted for age and gender are often within 1 SD of the mean, suggesting that reduced bone quality contributes significantly to their fracture risk (2). On bone biopsy, most patients with stage 5 CKD have renal osteodystrophy (ROD), with microarchitectural changes that are likely to reduce bone strength. Both fracture and ROD are components of the cluster now termed "chronic kidney disease mineral and bone disorder" (CKD-MBD).

After kidney transplantation, many laboratory features of CKD-MBD improve, but abnormally high and low levels of bone turnover are reported in bone biopsy studies (3,4). Loss of BMD is of particular concern in the first year after transplantation, when rapid declines may occur (5–11). Glucocorticoid treatment is the major contributor, but persisting hyperparathyroidism, suboptimal levels of 25-hydroxyvitamin D [25(OH)D], hypogonadism, hypophosphatemia, treatment with calcineurin inhibitors, and prolonged hospitalization may also contribute. In combination with residual changes of ROD and patient characteristics such as peripheral neuropathy, poor muscle strength, balance, visual acuity, and a propensity to fall, changes in BMD may contribute to incident fracture rates, reported to be 20% by 36 mo after transplantation (12).

Bisphosphonates, vitamin D analogues and calcitonin are all reported to prevent loss of BMD after kidney transplantation (13–18). Inclusion criteria for studies that assessed these drugs varied, with BMD T-scores ranging from 1.13 to −2.40 and some studies only documenting *Z*-scores, BMD (g/cm^2), or the proportion of patients with osteopenia or osteoporosis. In general, risk factors that influence treatment choices in the general population were not considered, and treatment was not guided by biochemical bone turnover markers or factors that are particular to patients with CKD. Few studies have assessed bone histomorphometry, but one randomized, controlled trial reported that 6 mo after transplantation, adynamic bone was present in all patients who were treated with pamidronate (19).

No study has been powered for patient-level outcomes, such

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as fracture or hospitalization. Recently published Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD guidelines for posttransplantation bone disease suggest BMD measurement in the first 3 mo after transplantation when patients have an estimated GFR of >30 ml/min per 1.73 m^2 and that treatment with vitamin D, calcitriol/alfacalcidol, or bisphosphonates be considered, targeting patients who are at higher fracture risk (20). However, at present there is no guidance to formulating such an individualized approach. In 2002 we commenced using a simple treatment algorithm that incorporates risk factors and laboratory and imaging data to target bisphosphonates to patients who are likely to have a greater risk for fracture and calcitriol to those who are likely to be at lower risk or have lower markers of bone turnover (21). In this prospective study, we report on the efficacy of this regimen during the subsequent 5 yr.

Materials and Methods

The study population consisted of patients who were admitted to Westmead Hospital, Sydney, between 2002 and 2007 for kidney or kidney-pancreas transplantation. Twelve patients with previous bisphosphonate exposure were excluded, and none had been treated with cinacalcet. All 153 patients who attended the clinic for treatment allocation and returned for follow-up at 12 mo were included in this analysis. Patients were allocated to bisphosphonate or calcitriol therapy according to an algorithm developed between 2000 and 2002 that incorporated laboratory investigations at 2 to 4 wk after transplant, when renal function had generally stabilized; BMD measured by dual-energy x-ray absorptiometry; evidence of vertebral fracture on the basis of lateral spine x-ray; and demographic data (Figure 1). Patients who were allocated to bisphosphonates were treated with oral alendronate 70 mg/wk; for patients with symptomatic gastroesophageal reflux, treatment was a single 4-mg intravenous dose of zoledronate. Patients who were allocated to calcitriol were treated with 0.25 μg twice daily, with dosage reduction when their levels of corrected serum calcium approached the upper range. Patients with levels of 25(OH)D <60 nmol/L were prescribed cholecalciferol at dosages that ranged from 1000 to 4000 IU/d. Calcium carbonate 600 mg/d was prescribed to patients with low dietary calcium intake on the basis of dietary assessment, provided that they did not have hypercalcemia or hypophosphatemia. When patients had divergent markers of bone formation (serum osteocalcin) and resorption (urinary deoxypyridinoline/creatinine; DPD/Cr), calcitriol was used when the osteocalcin level was below the assay normal range, as indicated in Figure 1. Although a placebo group was not included, BMD changes were calculated for 16 additional patients who underwent standard testing but did not attend for treatment allocation and did not receive calcitriol or bisphosphonate therapy.

Blood was collected on the morning of elective transplantations and immediately before cadaveric transplantations. Fasting morning samples were then collected at 2 to 4, 12, and 52 wk from transplantation. In addition to standard biochemical analyses, assays were performed for levels of 25(OH)D and calcitriol (DiaSorin) and, for women, follicle-stimulating hormone and luteinizing hormone (Axsym System; Abbott Laboratories). Intact parathyroid hormone (iPTH), estradiol (all patients), serum testosterone, sex hormone–binding globulin, and calculated free testosterone (for men) were assayed using the Immulite system (Diagnostic Products Corp). For osteocalcin, a two-site immunometric assay was used recognizing the intact molecule (Nichols Advantage). At 2 to 4, 12, and 52 wk, urinary levels of calcium, creatinine, and deoxypyridinoline (Immulite) were measured. BMD by dual-energy x-ray absorptiometry (Norland XR800) was measured within 2 wk of admission at the lumbar spine, femoral neck, and the distal radius and ulna. *Z*-scores were adjusted for age and gender using Geelong (Australia) data for women and Boston (MA) data for men. All patients underwent baseline and 1-yr lateral x-rays of the lumbar and thoracic spines, which were assessed by an experienced clinician and a radiologist without previous patient knowledge, using semiquantitative vertebral fracture criteria developed by Genant *et al.* (22). Any suspected fracture was assessed quantitatively and for inclusion was defined as a ≥20% reduction in vertebral height in the absence of degenerative change. Nonvertebral incident fractures were assessed by patient history and confirmed by review of the relevant x-ray, bone scan, or magnetic resonance imaging report.

Statistical Analysis

Differences from baseline to 1 yr between patients who were allocated to treatment with bisphosphonate or calcitriol were analyzed by independent sample *t* test or the Mann-Whitney *U* test for continuous data and the $\chi 2$ test for categorical data. Analysis was by intention to treat. Because no differences were detected for outcomes of patients who were treated with intravenous *versus* oral bisphosphonates, these data were analyzed together. Within-group differences in BMD from baseline to 1 yr were calculated using the paired *t* test. For determination of predictors of change in BMD, univariate analyses were performed using age at transplantation, gender, mode of dialysis, months on dialysis, history of parathyroidectomy, transplant type, bisphosphonate use in the first year after transplantation, pretransplantation estradiol and testosterone levels (men), menopausal status (women), 2- to 4-wk posttransplantation serum iPTH, alkaline phosphatase (ALP), osteocalcin, 25(OH)D, calcium, calcitriol, and the DPD-Cr ratio. Variables with $P \leq 0.1$ were included in the multivariate model. Continuous data are presented as means ± SEM (normal distribution) or median and range (non-normal distribution), and categorical data are presented as percentage. Normal distribution was examined using P-P plots. Analyses were performed using SPSS 16.0.1 for Macintosh.

Patients admitted to the transplant unit are informed that deidentified data are collected for clinical studies with approval of the local ethics committee. All investigations for this study were considered routine care for patients who were followed in the renal metabolic bone clinic.

Results

Patient characteristics at baseline are summarized by transplant type and treatment allocation in Table 1. Patients who received kidney-pancreas transplants were younger than kidney-only recipients, were more likely to receive a preemptive transplantation, were less likely to be on hemodialysis, had a shorter time on dialysis, and fewer had undergone parathyroidectomy. They had lower pretransplantation levels of calcium (2.35 ± 0.02 *versus* 2.43 ± 0.03; $P = 0.02$) and higher levels of iPTH (median 37.7 *versus* 20.0 pmol/L; $P = 0.007$) and ALP (median 114 *versus* 78 U/L; $P < 0.0001$). Their baseline BMD levels were lower at the femoral neck, lumbar spine, and wrist (Table 2).

Of the 153 transplant recipients, 95 (62%) were allocated to treatment with bisphosphonates and 58 (38%) to calcitriol. Patients who were allocated to bisphosphonates were less likely to receive a preemptive transplant and had longer periods on dialysis with hemodialysis as the more common dialysis mo-

STEP ONE: Early post-transplant BMD by DXA and lateral thoracic and lumbar spine radiographs.

STEP TWO: Laboratory investigations including PTH, 25(OH)D and markers of bone turnover; osteocalcin (Ost), alkaline phosphatase (ALP) and urinary deoxypyridinoline/creatinine ratio (DPD/Cr) at 2-4 weeks as renal function stabilizes.

STEP THREE: Score risk factors for fracture.

Age >50 years	1
Hypogonadal male or female	1
Previous non-vertebral fragility fracture	1
Prolonged oral glucocorticoids pre-transplant	1
Low body mass index	1
First degree relative with osteoporosis	1
Postural instability, peripheral neuropathy, reduced visual acuity, falls	1
Pre-transplant iPTH >50 pmol/L / osteitis fibrosa on bone biopsy	1
Type 1 diabetes	2

STEP FOUR: Allocate patients to bisphosphonate □or calcitriol ■therapy. Borderline patients ⚄ prescribed bisphosphonates for risk factor scores ≥3. Unless contraindicated, all patients receive cholecalciferol until vitamin D replete plus calcium supplementation. Patients with T-scores above 0 or with prior parathyroidectomy and low bone turnover receive or continue calcitriol.

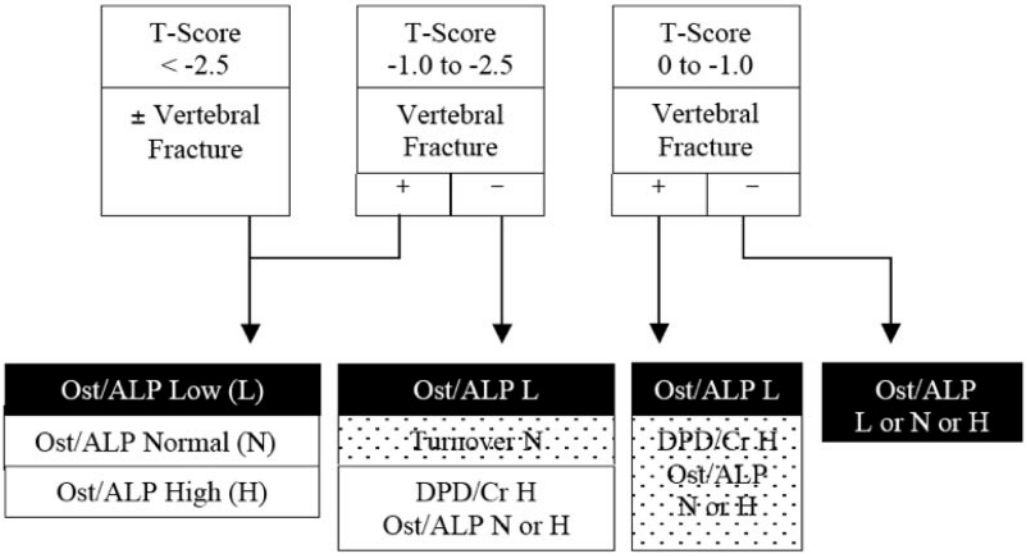

Figure 1. Algorithm for treatment allocation after transplantation. Adapted from reference (35).

dality (Table 1). As expected from the treatment algorithm, patients who were allocated to bisphosphonates had lower BMD at the lumbar spine and femoral neck than those who were allocated to calcitriol (Table 2), with mean T-scores of −0.61 *versus* 0.52 and −2.01 *versus* −0.58, respectively. Fifty-two percent of bisphosphonate-treated patients had prevalent vertebral fractures *versus* 11% who were allocated to calcitriol ($P < 0.0001$; Table 3). Assessed by transplant type and treatment allocation, patients who received bisphosphonates had higher *pretransplantation* levels of iPTH, ALP, and osteocalcin ($P \leq 0.05$), whereas levels of calcium, phosphate, 25(OH)D, and calcitriol did not differ. Differences in laboratory values at 2 to 4 wk after transplantation for patients who were allocated to calcitriol or bisphosphonate are presented in Table 3. Those who were treated with bisphosphonates had higher urinary DPD-Cr ratios ($P = 0.02$) and levels of ALP ($P = 0.006$) and serum calcium ($P = 0.03$). Two patients with suppressed 2- to 4-wk osteocalcin and ALP levels received bisphosphonates when levels increased by their clinic visit.

At 1 yr, serum creatinine levels were similar for bisphosphonate- and calcitriol-treated patients (120 ± 4 *versus* 131 ± 6 μmol/L, respectively; $P = 0.16$). Mean levels of calcium, phosphate, iPTH, ALP, urine DPD/Cr, and osteocalcin were within the normal range in both groups, although patients who received bisphosphonates had lower median levels of osteocalcin (3.6 *versus* 4.9 μg/L; $P = 0.02$) and higher median levels of iPTH

Table 1. Patient characteristics by treatment allocation and transplant type

Patient Characteristic	Treatment Allocation		Transplant Type	
	Bisphosphonate (n = 95)	Calcitriol (n = 58)	Kidney (n = 94)	Kidney-Pancreas (n = 59)
Age (yr; mean ± SD)	45 ± 11	43 ± 11	48 ± 12	39 ± 7[a]
Male (%)	63	48	62	51
Hemodialysis (%)	65	43[c]	65	44[b]
Peritoneal dialysis (%)	22	38	25	32
Preemptive transplant (%)	13	19[c]	10	24[b]
Time on dialysis (mo; median [range])	24 (0 to 402)	10 (0 to 280)[b]	24 (0 to 402)	9 (0 to 60)[a]
Parathyroidectomy (%)	7	16	15	3[b]
Kidney-only recipient (%)	57	69	–	–
Kidney-pancreas recipient (%)	43	31	–	–

Between-group differences: [a]$P \leq 0.0001$, [b]$P = 0.02$, [c]$P = 0.03$.

Table 2. Baseline and 1-yr BMD and *Z*-scores according to group

Parameter	Baseline		1-Year	
	BMD (g/cm^2)	*Z*-Score	BMD (g/cm^2)	*Z*-Score
Kidney				
lumbar spine	1.11 ± 0.02	0.38 ± 0.16	1.10 ± 0.03	0.34 ± 0.17
femoral neck	0.87 ± 0.02	−0.04 ± 0.15	0.85 ± 0.02	−0.17 ± 0.15
wrist	0.35 ± 0.01	0.18 ± 0.21	0.36 ± 0.01	−0.03 ± 0.21[a]
Kidney pancreas				
lumbar spine	1.04 ± 0.02[a]	−0.33 ± 0.15[b]	1.05 ± 0.02	−0.23 ± 0.15
femoral neck	0.77 ± 0.02[a]	−1.22 ± 0.15[b]	0.80 ± 0.02	−1.08 ± 0.15[c]
wrist	0.30 ± 0.01[a]	−0.64 ± 0.24[a]	0.30 ± 0.01	−0.83 ± 0.19
Bisphosphonate				
lumbar spine	1.02 ± 0.02[d]	−0.29 ± 0.14[d]	1.05 ± 0.02[d]	−0.17 ± 0.14
femoral neck	0.77 ± 0.01[d]	−1.01 ± 0.12[d]	0.78 ± 0.01[a]	−0.92 ± 0.13
wrist	0.32 ± 0.01	−0.47 ± 0.21[a]	0.31 ± 0.01	−0.68 ± 0.20[a]
Calcitriol				
lumbar spine	1.18 ± 0.03	0.77 ± 0.18	1.14 ± 0.03	0.61 ± 0.22
femoral neck	0.92 ± 0.02	0.35 ± 0.19	0.91 ± 0.02	0.14 ± 0.19
wrist	0.36 ± 0.01	0.33 ± 0.23	0.37 ± 0.01	0.15 ± 0.20

Kidney pancreas recipients had lower baseline BMD and *Z*-scores than kidney recipients. Patients who were allocated to bisphosphonates had lower BMD (spine and hip) and *Z*-scores (all sites) than those who were allocated to calcitriol. After bisphosphonates, 1-yr BMD improved at the lumbar spine (3.3 ± 0.9%; 95% confidence interval 1.5 to 5.1%) and femoral neck (2.0 ± 0.8%; 95% confidence interval 0.4 to 3.6%). Z-scores decreased at the wrist in kidney recipients and those who were allocated to bisphosphonates and improved at the femoral neck in kidney-pancreas recipients.

[a]$P \leq 0.05$, [b]$P \leq 0.001$, [c]$P = 0.01$, [d]$P \leq 0.0001$.

(8.3 *versus* 5.6 pmol/L; $P = 0.007$; Table 3). For patients who received bisphosphonates *versus* calcitriol, incident fracture at any location occurred in 13 *versus* 9% ($P = 0.52$) and incident vertebral fracture occurred in 10 *versus* 2% ($P = 0.15$). For patients who were allocated to bisphosphonates, BMD increased significantly at the lumbar spine and femoral neck, whereas for patients who were allocated to calcitriol, there were no significant changes in BMD at any site (Table 2). In multivariate analysis, each 10-mo period of dialysis before transplantation predicted a change in lumbar spine BMD during the ensuing year of −0.4% (95% confidence interval −0.7 to −0.1%; $P = 0.006$). At the femoral neck, male gender predicted increased BMD in the first posttransplantation year, with a trend to increased BMD when calcitriol levels were higher ($P = 0.054$). No variable predicted change in BMD at the wrist. For patients who were allocated to calcitriol, baseline BMD correlated positively to change in BMD during the ensuing year ($P = 0.009$), and lower BMD at the lumbar spine predicted (nonver-

Table 3. Biochemical and fracture data at 2 to 4 wk and 1 yr after transplantation

Parameter	2 to 4 Wk				1 Yr			
	Transplant Type		Treatment Received		Transplant Type		Treatment Received	
	K	KP	BP	C	K	KP	BP	C
Calcium (2.13 to 2.63 mmol/L; mean ± SE)	2.40 ± 0.02	2.41 ± 0.02	2.43 ± 0.02[a]	2.37 ± 0.02	2.42 ± 0.02	2.40 ± 0.02	2.42 ± 0.02	2.41 ± 0.02
Phosphate (0.65 to 1.05 mmol/L; mean ± SE)	0.82 ± 0.03	0.80 ± 0.04	0.79 ± 0.03	0.86 ± 0.04	1.03 ± 0.03	0.98 ± 0.04	1.00 ± 0.03	1.03 ± 0.03
iPTH (1.0 to 6.8 pmol/L; median [range])	10.5 (0 to 167)	10.5 (1 to 209)	10.1 (0 to 167)	11.3 (0 to 209)	7.5 (0 to 394)	7.0 (2 to 70)	8.3 (0 to 394)[b]	5.6 (0 to 31)
Osteocalcin (3.7 to 10.0 μg/L; median [range])	4.5 (1 to 55)	4.7 (0.7 to 32)	5.5 (1 to 55)	3.6 (1 to 26)	4.8 (1 to 45)	4.1 (1 to 17)	3.6 (1 to 32)[a]	4.9 (1 to 45)
ALP (30 to 115 U/L; median [range])	82 (20 to 425)	94 (39 to 352)	95 (20 to 425)[b]	78 (38 to 363)	72 (29 to 221)	64 (35 to 341)	69 (37 to 341)	69 (29 to 221)
Urinary DPD/Cr (2.3 to 5.4 nmol/mmol male, 3.0 to 7.4 nmol/mmol female; mean ± SE)	7.8 ± 0.4	9.4 ± 0.5[a]	8.9 ± 0.4[a]	7.5 ± 0.4	5.1 ± 0.4	4.9 ± 0.3	4.9 ± 0.3	5.2 ± 0.4
25(OH)D (31 to 107 nmol/L; mean ± SE)	54 ± 2	38 ± 2[a]	48 ± 2	48 ± 3	65 ± 3	66 ± 4	63 ± 3	70 ± 4
Calcitriol (36 to 120 pmol/L; mean ± SE)	95 ± 7	78 ± 8	94 ± 8	85 ± 7	132 ± 8	115 ± 9	126 ± 8	125 ± 9
Prevalent vertebral fracture (%)	32	45	52	11[a]	–	–	–	–
Incident fracture, any site (%)	–	–	–	–	9	16	13	9
Incident vertebral fracture (%)	–	–	–	–	6	9	10	2

BP, bisphosphonate; C, calcitriol; K, kidney; KP, kidney-pancreas.
[a]$P \leq 0.05$, [b]$P \leq 0.01$ for comparison.

tebral) incident fracture ($P = 0.028$). Conversely, for patients who were allocated to bisphosphonates, baseline BMD did not predict incident fracture or change in BMD.

Sixteen patients who underwent BMD testing at baseline and 1 yr were not seen at the clinic and did not receive bisphosphonate or calcitriol therapy. The BMD of these patients fell at the lumbar spine from 1.14 ± 0.16 to 1.07 ± 0.18 g/cm^2 ($P = 0.001$), at the femoral neck from 0.88 ± 0.16 to 0.79 ± 0.09 g/cm^2 ($P = 0.011$), and at the wrist from 0.36 ± 0.07 to 0.35 ± 0.07 g/cm^2 ($P = 0.243$).

Acute rejection occurred in 29% of patients with no difference between treatment groups. Acute rejection was more common in kidney-pancreas recipients (40 *versus* 22%; $P = 0.03$), although this group had lower levels of serum creatinine at 1 yr (107 ± 4 *versus* 135 ± 5 μmol/L; $P < 0.0001$). Three months after transplantation, the fasting urinary calcium-creatinine ratio for patients who were allocated to calcitriol and bisphosphonate did not differ (0.25 *versus* 0.23 mmol/mmol creatinine, respectively; $P = 0.43$), whereas at 1 yr the ratios differed (0.25 *versus* 0.20 mmol/mmol creatinine; $P = 0.03$). At 1 yr, there were no treatment group differences for incidence of hypercalcemia (serum calcium $\geq$2.63 mmol/L; bisphosphonate 10 *versus* calcitriol 8%; $P = 0.61$). Three patients who were taking calcitriol commenced treatment at a lower 0.25-μg/d dosage because of borderline hypercalcemia; one stopped treatment at 6 mo, and eight had a dosage reduction by their treating renal physician. Eleven were on dosages >0.5 μg/d at 12 mo, including some with previous parathyroidectomy. Of patients who were treated with bisphosphonates, one stopped because of back pain, one stopped because of bone pain, two omitted tablets for 2 to 3 mo, and one took the medication with milk. Five patients were treated with intravenous bisphosphonate because of symptomatic reflux or peptic ulcer disease.

Discussion

The algorithm used for treatment allocation in this study incorporates risk factors that influence osteoporotic fracture in the general community, such as BMD and prevalent vertebral fracture. It also includes potential risk factors that are specific to renal transplantation, such as the risk that patients with low bone turnover soon after transplantation may develop adynamic bone if allocated to bisphosphonate therapy. Patients with normal bone formation markers and osteopenia and without prevalent vertebral fracture were considered borderline for bisphosphonate therapy, as were patients with a T score of -1 to 0 plus prevalent vertebral fracture. For these patients, we assessed factors that have been associated with increased fracture risk in the general community: History of nonvertebral fragility fracture, presence of hypogonadism, low body mass index, postural instability, reduced visual acuity, falls, and family history of osteoporosis. We also assessed factors that are of particular relevance to patients with CKD, including levels of PTH, previous glucocorticoid exposure, the presence of diabetes, and peripheral neuropathy.

A number of assumptions underscore this algorithm: That patients with prevalent fracture and BMD levels in the osteopenic or osteoporotic range may have better protection against BMD loss with bisphosphonates than calcitriol; that when BMD is near normal and bone turnover is low, bisphosphonates are less likely to be effective; and that treatment with calcitriol might improve mineralization and also limit BMD loss but with less potential to induce low bone turnover or adynamic bone. Consequently, bisphosphonate-treated patients, who were deemed to be at higher fracture risk, generally had lower BMD, higher bone turnover markers, and higher rates of prevalent fracture. BMD levels increased at the lumbar spine and hip in these patients, but 13% had incident fractures. Patients who were allocated to calcitriol had higher pretransplantation BMD levels, which remained stable at each site, and these patients had an incident fracture rate of 9%. At 12 mo, mean levels of bone turnover markers were normal in both groups. Although bone biopsies were not performed, these results suggest that targeted therapy is unlikely to induce low turnover or adynamic bone.

Previous studies of renal transplant patients have used calcitriol dosages in the range of 0.25 to 0.50 μg/d. We chose a dosage of 0.25 μg twice daily on the basis of previous renal transplant studies (23,24) and studies that used calcitriol to prevent loss of BMD in other solid-organ transplants (25,26). Some subsequent renal transplant studies have used similar regimens (17,27).

Historically, BMD loss is common after kidney transplantation. Julian *et al.* (8) documented 6.8% reduction in BMD at the lumbar spine at 6 mo and 8.8% at 18 mo, and Casez *et al.* (5) described 7% reduction in BMD at the lumbar spine within 24 wk and 4.3% at the hip within 36 wk of transplantation. A number of subsequent studies reported that treatment with bisphosphonate or calcitriol and its analogues attenuated BMD loss after kidney transplantation compared with placebo (19,28–31). The meta-analysis of Palmer *et al.* (32) assessed 24 randomized, controlled kidney transplant trials and summarized effects of bisphosphonates, vitamin D and its analogues, and calcitonin on BMD. At the femoral neck and lumbar spine, two studies favored bisphosphonates over calcitriol, with both bisphosphonates and vitamin D or its analogues superior to placebo. For calcitonin, only lumbar spine BMD showed improvement, and a single trial that compared calcitonin with bisphosphonates did not report differences between groups. Significant heterogeneity existed in some of these analyses, related to differences in baseline BMD and timing of treatment initiation. No therapy resulted in significant fracture prevention. Most recently, Walsh *et al.* (18) studied 93 kidney transplant recipients who had *Z*-scores above -1.5 and PTH levels of >150 pg/ml and were randomly assigned to intravenous placebo or pamidronate 1 mg/kg at baseline and at 1, 4, 8, and 12 mo. In the pamidronate group, lumbar spine BMD increased by 2.1%, but BMD decreased at the total hip and femoral neck by 0.4 and 0.2%, respectively. Patients who were allocated to placebo had reductions in BMD at the lumbar spine, total hip, and femoral neck of 5.7, 4.4, and 2.6%, respectively. Nevertheless, bisphosphonate use remains controversial. Major concerns include prolonged duration of effect because of reduced renal clearance; the possibility of perpetuating or inducing adynamic bone disease, which could increase fracture risk (33); exacerba-

tion of secondary hyperparathyroidism; and a lack of proven patient-level benefit. Despite the increased risk for fracture after kidney transplantation, no study has yet demonstrated that preservation of BMD prevents fracture, although the study of Akaberi *et al.* (34) did report an association between fracture and osteopenia, or a BMD <0.9 g/cm^2 at the hip. In this context, preservation of BMD might be regarded as an "acceptable outcome" provided that it is achieved with a low risk for adverse effects, is unlikely to result in low bone turnover, and, in the absence of proven patient-level benefits, if treatment allocation is stratified according to perceived fracture risk. This was the focus of our study.

This study does have a number of limitations. Treatment groups differed, because rather than being a head-to-head comparison of bisphosphonates and calcitriol, our aim was to show that individualized therapy prevented BMD loss and allowed bone turnover markers to normalize without adverse events. Second, because historical and recent data confirm that BMD levels fall after transplantation, a placebo group was not included; however, a group of patients who did not receive treatment allocation were included as a comparator. This group had similar reductions in BMD to placebo-treated patients in other studies. Another potential concern is that treatment allocation occurred up to 6 wk after transplantation, during which time glucocorticoid exposure was high. We were unable to shorten this time, because levels of the turnover markers and the PTH assay used vary with renal function and because of laboratory turnaround times. Markers such as bone-specific ALP, TRAcP-5B, and PTH(1–84), which do not fluctuate with renal function, may allow earlier allocation. In relation to the risk factor analysis, we would now include any fracture not involving face, fingers, or toes rather than "fragility" fracture, which is open to misallocation. Finally, although this algorithm can provide guidance and alert the clinician to factors that might not otherwise have been considered, it cannot replace clinical judgment and discussion of therapeutic options with patients.

Calculators that incorporate demographic, laboratory, and imaging data have recently become available for estimating individual fracture risk and better targeting therapy in the general population (http://www.shef.ac.uk/FRAX/; http://www.garvan.org.au/promotions/bone-fracture-risk/). Similarly, the algorithm used in this study incorporates risk assessment using a variety of easily accessible data and alerts the clinician to potential contributors to fracture risk while helping to individualize therapy. This approach is supported by recent KDIGO CKD-MBD recommendations for managing bone disease after renal transplantation, and this article provides the first guide to how these recommendations might be implemented. Although use of this algorithm maintains levels of BMD and minimizes assessable risks, for the management of posttransplantation bone disease to advance, further studies are required. These should be randomized, controlled trials that assess the impact of bisphosphonates, calcitriol and its analogues, and newer bone-active drugs over at least 1 yr on end points such as bone histomorphometry and with sufficient power to assess patient-level outcomes of quality of life and fracture.

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Disclosures

None.

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