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Review Article

Review article: Managing bone complications after kidney transplantation

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SUMMARY: Chronic kidney disease mineral and bone disorder (CKD-MBD) describes the laboratory, bone and vascular abnormalities that exist in patients with CKD stages 3–5D and that may persist after transplantation. Persisting abnormalities of bone turnover and abnormal mineralization, together with bone mineral density (BMD) loss from glucocorticoids, may all predispose to a loss of structural integrity and increased fracture risk in kidney and kidney pancreas recipients. Vitamin D, calcitriol, calcitonin and bisphosphonates have all been used to preserve BMD following transplantation, despite a lack of safety data and the potential for some of these drugs to cause harm. A limited number of post-transplant studies utilizing these drugs have not yet documented improved fracture prevention or fracture-related mortality and have not considered allocation based on risk factors for fracture or markers of bone turnover. Targeted allocation of the available therapies based on a stratification of risk appears warranted. This might be achieved using an algorithm incorporating BMD, X-ray evaluation, laboratory investigations including bone turnover markers and the assessment of standard fracture risk factors at the time of and soon after transplantation. This approach, which is similar to protocols used in the general population, may result in more effective management of patients and fewer adverse effects such as adynamic bone disease. Although BMD is a surrogate for fracture risk in the general population it is not validated in this transplant population. Consequently, such an approach should be confirmed by studies that include bone biopsy data and an evaluation of patient level outcomes.

KEY WORDS: **algorithm, bisphosphonate, bone mineral density, bone turnover, calcitriol, kidney transplant.**

INTRODUCTION

It has been over 50 years since the first kidney transplant was performed. Since then, the evolution of immunosuppression has led to an improvement in graft and patient survival, so that death with a functioning graft is now the most common cause of graft failure (ANZDATA, http://www.anzdata.org.au). All patients undergoing kidney or kidney pancreas transplantation have abnormalities described by the term 'chronic kidney disease mineral and bone disorder' (CKD-MBD). Features of this cluster of interwoven laboratory, bone and vascular abnormalities often persist after transplantation when graft function is poor, but in many cases when function is excellent. In addition, glucocorticoid exposure predisposes to reduction in bone mineral density (BMD) and high rates of fracture.

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Managing CKD-MBD associated with low BMD after transplantation is challenging and is generally undertaken without information available from bone histomorphometry. Surprisingly, data often used to inform treatment decisions when community patients are assessed following a fracture or the discovery of low BMD by dual-energy X-ray absorptiometry (DXA), tend to be overlooked after renal transplantation. However, a careful history, noninvasive laboratory investigations and simple radiological tests may help target treatment more effectively. Biochemical evaluation of bone turnover markers may be useful in these patients, but requires careful interpretation. Bone histomorphometry with double tetracycline labelling provides the most accurate assessment of bone turnover. Both high and low turnover have been reported in the limited bone biopsy studies that have been performed after renal transplantation.[1,2]

CHANGES TO BMD AND RATES OF FRACTURE FOLLOWING RENAL TRANSPLANTATION

Historically, BMD loss is common after kidney transplantation. Julian and co-workers documented a 6.8% loss of BMD

at the lumbar spine at 6 months and 8.8% at 18 months[3] and Casez and co-workers described losses in BMD of 7% at the lumbar spine within 24 weeks and 4.3% at the total hip within 36 weeks of transplantation.[4] However, Mikuls and co-workers reported a BMD loss of only 2.4% at the lumbar spine with no significant change at the femoral neck.[5] No patients in these studies were treated with vitamin D or bisphosphonates. Brandenburg *et al.* reported a 2.8% lumbar spine BMD loss at 1 year and stabilization of BMD by 6 years post-transplant.[6] A small number of patients (15%) were managed with either calcitriol or cholecalciferol during the follow-up period, but none was prescribed bisphosphonates. Recent studies have depicted quite divergent long-term BMD outcomes of continued loss, no change or overall gain. Casez and co-workers reported that in two-thirds of their patients, BMD at the lumbar spine underwent initial loss, followed by gradual gain at 6 months post-transplant (4). However, in 25% of patients BMD at the limbs, spine and trunk continued to worsen over a 75-week follow-up period. Marcen and co-workers observed similar findings in 86 renal-transplant recipients. At 1 year, approximately one-third of patients had preservation of lumbar spine BMD, one-third gained BMD with a mean change of 9% and one-third lost BMD with a mean reduction of 5.5%.[7] A cross-sectional analysis of 59 long-term (>5 years) renal transplant recipients revealed 53% of patients met WHO criteria for osteoporosis and 44% had prevalent vertebral and non-vertebral fractures.[8] Patients with non-vertebral fractures had a 77% prevalence of osteoporosis compared with a 45% prevalence in those without fractures ($P < 0.05$), while surprisingly, vertebral fractures were not associated with low BMD. A positive correlation was described between cyclosporine dosage and femoral neck or lumbar spine BMD. None of these analyses were adjusted for potential confounders and timing of fracture occurrence was not detailed.[8]

For kidney transplant recipients, fracture rates are higher than for patients on dialysis, which in turn are above rates in the general community. Using the United States Renal Data System (USRDS) to identify new Caucasian dialysis patients (not age limited) between 1989 and end 1996, the incidence of hip fracture was 7.45 per 1000 person years for males and 13.63 per 1000 person years for females.[9] When compared with people of the same sex in the general population, the overall relative risk (RR) for hip fracture was 4.44 (95% CI 4.16 to 4.75) for male dialysis patients and 4.40 (95% CI 4.17 to 4.64) for female dialysis patients. For patients on dialysis, fracture is independently predicted by risk factors that are applicable to the general population; increasing age, female sex, reduced body mass index and the presence of peripheral vascular disease.[10] Ball *et al.* used the USRDS to determine hip fracture rates for patients of any race but age ≤70 years on dialysis and after transplantation.[11] Rates were 2.9 and 3.3 per 1000 patients per year for those on dialysis and transplant recipients, respectively. After adjustment for age, gender, diabetic nephropathy and time on dialysis, transplant patients had a 34% increase in fracture risk compared with patients who remained on dialysis. Each month following engraftment this risk decreased by 1% and by 630 days was equal to that of dialysis patients.[11] Ramsey-Goldman described a cohort of 432 kidney transplant recipients followed for up 2 years post-transplant. The fracture rate in these patients was lower than generally reported at 3.9 per 100 patient years and occurred most commonly at the foot within the first 2 years after transplantation.[12]

In addition to the standard risk factors mentioned above, many factors that influence bone quality are likely to contribute to post-transplant fracture risk. These include residual changes of renal osteodystrophy, glucocorticoid dose, persisting hyperparathyroidism, suboptimal levels of 25-hydroxyvitamin D [25(OH)D], hypogonadism, hypophosphatemia, treatment with calcineurin inhibitors and prolonged hospitalization. Reduced BMD is clearly a major contributor to fracture risk in the general community and is reported to be associated with fracture for patients about to undergo renal transplantation,[13] although for patients on dialysis the association is less well established. A recent meta-analysis summarizing 6 observational studies with 683 hemodialysis patients attempted to clarify the relationship.[14] Patients with a history of fragility or vertebral fracture had lower BMD at the lumbar spine, mid-, one-third and ultra-distal radius compared with those without fracture. Lower BMD at the femoral neck was not associated with fracture occurrence. However, the quality of included studies was poor and significant heterogeneity, which was not investigated by the study authors, was present in most analyses.[14]

Glucocorticoids have an established causal role in reducing BMD and increasing fracture risk. These drugs decrease osteoblast proliferation and increase apoptosis while accelerating osteoclastogenesis. This leads to an increase in bone resorption while reducing intestinal and renal calcium reabsorption and exacerbates the risk of secondary hyperparathyroidism. Two randomized controlled trials have assessed the effect of glucocorticoids on BMD after renal transplantation. In the FREEDOM trial, *de novo* renal transplant recipients who underwent steroid avoidance or early steroid withdrawal were not found to have significant differences in hip or lumbar spine BMD compared with standard steroid usage.[15] At 1-year post-transplant, lumbar spine BMD fell slightly in all three groups while femoral neck BMD decreased insignificantly in the standard steroid group only. In another study, steroid withdrawal more than 5 years post-transplant was associated with an increase in BMD over the following year of 2.5% at the lumbar spine and an increase at the hip (with the per cent change not specified), compared with patients who continued on prednisone at a mean dose of 5.9 mg/day.[16] This cohort was young (mean age 44 years), mostly male and only 4% suffered from diabetes.

Levels of parathyroid hormone decrease rapidly after successful transplantation as fragments are cleared with an improvement in Glomerular Filtration Rate (GFR), but persistent hyperparathyroidism is common and can cause hypercalcaemia, worsen hypophosphataemia and exacerbate bone loss by increasing bone turnover. Messa *et al.* have described changes to levels of intact-parathyroid hormone (iPTH) in 81 renal transplant recipients.[17] Although levels fell at 3 months, mean values remained

elevated at 17.2 pmol/L (normal range to 8.4 pmol/L) at 12 months. Patients with elevated iPTH were older, spent longer on dialysis prior to transplant and had higher pre-transplant iPTH levels. Nevertheless, 12-month levels of serum calcium and phosphate were similar for those with normal and elevated levels of iPTH. A subgroup of patients with elevated iPTH and hypercalcaemia (ionized calcium 1.46 ± 1.05 mmol/L) underwent further investigation and was found to have a higher PTH calcium set-point. Secondary hyperparathyroidism is reported to be present in over 30% of patients more than 3 years post-transplant and has been associated with reduced BMD at the hip.[18]

Bone biopsy with double tetracycline labelling is the only accurate and reasonably available means of diagnosing the histopathology of post-transplant bone disease, but is performed infrequently. A number of important observations can be made from the few available post-transplant bone biopsy studies.[1,2,19] From 5% to 16% of patients are reported to have normal bone histomorphometry, with normal bone volume and turnover reported in 28%. Changes of mixed renal osteodystrophy are reported most commonly, while adynamic bone disease or osteomalacia is present in 20–37%. A negative association has been reported between cumulative prednisone dosage and bone volume and turnover.[1]

QUALITY OF LIFE AND MORTALITY RISK AFTER FRACTURE

In the general population, osteoporotic fractures are associated with reduced quality of life, increased morbidity and mortality and increased health care costs. A large Canadian study of over 4800 men and women aged 50 years or more has provided data on health-related quality of life following either osteoporotic fracture or subclinical vertebral fracture, compared with those without fracture.[20] Following either of these two events, quality of life was significantly lower. Following hip fracture, mortality was significantly higher than age and gender matched controls; 4.5% higher 1 month post-fracture and 9% higher by 6 years. In the fracture group, 36% felt uncomfortable walking outdoors alone and 27% were residing in a chronic care hospital at the end of the follow-up period (mean 7 years). Kanis *et al.* reported that, compared with the general population, there was a higher RR of mortality 6 and 12 months after a vertebral fracture in males and females over the age of 50 years.[21] At 6 and 12 months the risk was 13.6 and 7.8 respectively for a 50-year-old man, decreasing to 1.8 and 0.99 respectively by the age of 90, with similar rates for women. For patients with CKD, an estimated GFR (eGFR) of <45 mL/min per 1.73 m^2 was associated with an almost twofold increase in hip-fracture-related mortality over a median follow-up of 7.25 years.[22] In an analysis of patients on dialysis with hip fracture, an approximate doubling of mortality was seen compared with nondialysis patients (42% and 61% for male and female dialysis patients, respectively).[23] After kidney transplantation this increased risk persists. In the first three post-transplant years, recipients hospitalized for hip fracture are reported to have increased all-cause mortality with a hazard ratio of 1.60 (95% CI 1.13 to 2.26) in Cox Regression analysis.[24]

ASSESSMENT OF BONE TURNOVER

Biochemical markers that measure bone turnover can be of clinical importance when interpreted accurately and in the appropriate patient population. Bone-specific alkaline phosphatase is an osteoblast product that can be used to assess bone formation and is not influenced by renal function. On the other hand, osteocalcin is produced by mature osteoblasts, incorporated into bone matrix and released during bone resorption, so levels reflect bone formation and overall turnover. Osteocalcin levels are influenced by renal clearance, glucocorticoid and calcitriol usage and like other turnover markers undergo diurnal variation. Byproducts of bone resorption and collagen breakdown by osteoclasts can also be measured in serum and urine. However, some resorption markers such as the urinary deoxypyridinoline/creatinine ratio are dependent on glomerular filtration and may be inaccurate in patients with unstable or impaired renal function.

MANAGEMENT OF LOW BMD AFTER KIDNEY TRANSPLANTATION

For the treatment of osteoporosis in the general population, a number of drugs are available that reduce BMD loss and the rate of incident fractures. For instance, bisphosphonates improve BMD, reduce hip fracture rates and decrease mortality in post-menopausal women.[25] Because of a lack of data on safety and an increased risk of adverse effects, the use of these drugs is controversial in patients with CKD and abnormalities of PTH or vitamin D, an eGFR <30 mL/min per 1.73 m^2 (stages 4–5) and after transplantation. Nevertheless, the efficacy of short and long term bisphosphonate treatment after renal transplantation has been examined.[26–31] These studies did not consider risk factors for fracture, markers of bone turnover or factors particular to patients with CKD, such as persisting hyperparathyroidism. Integrating a more targeted approach to treatment, based on an assessment of fracture risk might be more appropriate.

A recent meta-analysis of 24 randomized controlled trials summarized effects of bisphosphonates, vitamin D and calcitonin on bone after kidney transplantation.[31] Two studies favoured bisphosphonates over calcitriol when examining change in BMD at the femoral neck and lumbar spine. Compared with placebo, bisphosphonates and vitamin D increased lumbar spine and femoral neck BMD, while calcitonin improved lumbar spine BMD only. A single trial that compared calcitonin to bisphosphonates did not reveal any difference in BMD between groups. Significant heterogeneity existed in certain analyses (bisphosphonate *vs* placebo) related to differences in baseline BMD levels and timing of treatment initiation. No therapy was found to prevent fracture.[31] Trabulus and co-workers recently examined effects of alendronate, alfacalcidol and the combina-

STEP ONE: Pretransplant laboratory investigation including PTH. Early post-transplant BMD by DXA and lateral spine radiographs.

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

STEP THREE: Score other 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 and patients with T-scores above 0 are allocated to calcitriol.

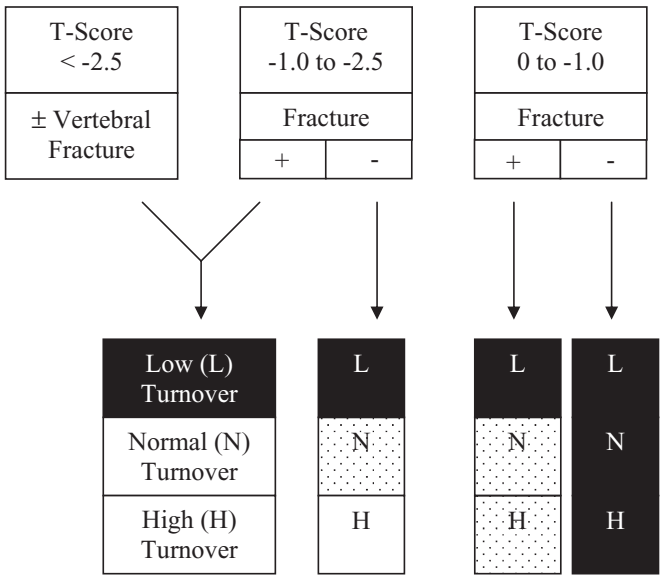

Fig. 1 Algorithm for treatment allocation after transplantation.[33] BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; iPTH, intact-parathyroid hormone.

tion.[27] Follow-up ranged from 1 to 179 months and with combination therapy, BMD increased at the lumbar spine and femoral neck by 7.9% and 8%, respectively. Alendronate monotherapy led to non-significant 4.4% and 6.5% gains at the lumbar spine and femoral neck respectively, while alfacalcidol led to non-significant changes of 0.7% at the lumbar spine and −1.8% at the femoral neck.[27] El-Agroudy and co-workers randomized 60 new transplant recipients to treatment with alfacalcidol, alendronate, calcitonin or no treatment, with follow-up to 1 year.[30] Patients may have been at relatively low risk for BMD loss with mean age 31 years, relatively short periods on dialysis and low rates of pre-existing BMD in the osteoporotic range. Treatment groups showed no change or slight improvement in BMD and in the non-treatment group, BMD decreased at the femoral neck. Nayak showed that weekly risedronate, in addition to calcium and vitamin D3 immediately after transplantation, preserved bone mass at 6 months.[28] BMD remained stable at both the femur and spine in those treated with a bisphosphonate while non-significant losses were observed in the control group. Similar effects are reported in studies up to 1-year post-transplantation. Kidney transplant

recipients with osteopenia or osteoporosis were treated with bisphosphonates for 6–12 months while those with normal BMD were not.[29] At 1-year post-transplant, patients who received bisphosphonates had an improvement in T-scores from −2.22 to −1.89 at the lumbar spine and a non-significant reduction in BMD at the total hip from −1.56 to −1.63. Those not treated lost BMD predominately at the lumbar spine (T-score −0.26 to −1.20). Despite these studies, bisphosphonate treatment 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, exacerbation of secondary hyperparathyroidism and a lack of proven patient-level benefit.[32]

TARGETED THERAPY TO REDUCE BONE COMPLICATIONS

Because patient level benefits of BMD preserving treatments are unproven and there is potential to cause harm, targeted treatment of patients at higher fracture risk would seem preferable. However, in a post-transplant setting, individualized assessment is time consuming and requires experience. One approach, which might reduce the risks of non-targeted regimens, is to use a treatment algorithm incorporating risk factors assessed at the time of transplantation and soon thereafter, to guide the allocation of bisphosphonates or calcitriol therapy (Fig. 1). In addition to BMD by DXA, this suggested algorithm includes a radiograph of the lateral thoracic and lumbar spine to assess for prevalent vertebral fracture, and once renal function stabilizes, measurement of 25(OH)D, iPTH and biochemical markers of bone-turnover; fasting serum osteocalcin and a second morning urine sample for deoxypyridinoline/creatinine. Using the algorithm, patients considered at high risk of fracture would generally be allocated to bisphosphonates; the allocation criteria being osteopenia or osteoporosis, prevalent vertebral fractures and normal or elevated bone turnover. On the other hand, patients with normal BMD or evidence of low bone turnover would generally be managed with calcitriol. We used this approach, in a prospective study of 155 kidney and kidney pancreas transplant recipients with 12-month follow-up.[33] Patients allocated to bisphosphonates had improved BMD at the lumbar spine of $4.9 \pm 1.7\%$ (95% CI 1.6% to 8.2%; $P = 0.004$) and stable BMD at the femoral neck and wrist, while calcitriol-treated patients had no significant change in BMD at any site. At 12 months, mean levels of calcium, phosphate, iPTH, ALP, osteocalcin and the urinary deoxypyridinoline/creatinine ratio were within the normal range in both treatment groups, and hypercalcemia (≥2.63 mmol/L) at 1 year post-transplant did not differ for those allocated to bisphosphonate or to calcitriol ($P = 0.61$). Patients receiving bisphosphonates had higher prevalent fracture rates and when compared with those treated with calcitriol, incident fracture at any location occurred in 13% *vs* 9% ($P = 0.52$), while incident vertebral fracture occurred in 10% *vs* 2%, ($P = 0.15$). No adverse effects were documented in either group.[33]

CONCLUSION

Improved graft outcomes and longer survival in an ageing transplant population predispose these patients to morbidity caused by metabolic bone disease. Renal osteodystrophy at the time of engraftment and reductions in BMD post-transplant are likely to contribute to the high fracture risk among these patients. Therapy with bisphosphonates or calcitriol is suggested for consideration in the soon to be published Kidney Disease Improving Global Outcomes recommendations, as is the targeting of therapy to reduce potential risks associated with treatment. Such a risk-based approach is similar to strategies used in the general population. Preliminary data suggest that such an approach is effective in maintaining or improving BMD with a reduced likelihood of adverse consequences because of suppressed bone turnover. For treatment of post-transplant bone disease to advance, future studies should include bone biopsy data or enroll sufficient subjects for patient level outcomes, particularly fractures, to be evaluated.

KEY POINTS

- Recipients of kidney transplants have varying degrees of CKD MBD
- BMD loss is common post-transplant and fracture risk is high
- Morbidity and mortality is elevated following fracture
- Prophylactic therapy is controversial because of underlying MBD, often impaired renal function and a lack of clinical outcome studies
- As in the general population, fracture risk and the likelihood of adverse treatment effects should be considered
- BMD by DXA, spine radiographs and biochemical bone turnover markers may assist in guiding therapy

REFERENCES

1. Monier-faugere MC, Mawad H, Qi Q, Friedler RM, Malluche HH. High prevalence of low bone turnover and occurrence of osteomalacia after kidney transplantation. *J. Amer. Soc. Nephrology* 2000; **11**: 1093–9.
2. Rojas E, Carlini R, Clesca P *et al*. The pathogenesis of osteodystrophy after renal transplantation as detected by early alterations in bone remodeling. *Kidney Int*. 2003; **63**: 1915–23.
3. Julian BA, Laskow DA, Dubovsky J, Dubovsky EV, Curtis JJ, Quarles LD. Rapid loss of vertebral mineral density after renal transplantation. *N. Engl. J. Med*. 1991; **325**: 544–50.
4. Casez JP, Lippuner K, Horber FF, Montandon A, Jaeger P. Changes in bone mineral density over 18 months following kidney transplantation: The respective roles of prednisone and parathyroid hormone. *Nephrol. Dial. Transpl*. 2002; **17**: 1318–26.
5. Mikuls TR, Julian BA, Bartolucci A, Saag KG. Bone mineral density changes within six months of renal transplantation. *Transplantation* 2003; **75**: 49–54.
6. Brandenburg VM, Politt D, Ketteler M *et al*. Early rapid loss followed by long-term consolidation characterizes the development

of lumbar bone mineral density after kidney transplantation. *Transplantation* 2004; **77**: 1566–71.
7. Marcen R, Caballero C, Pascual J *et al*. Lumbar bone mineral density in renal transplant patients on neoral and tacrolimus: A four-year prospective study. *Transplantation* 2006; **81**: 826–31.
8. Durieux S, Mercadal L, Orcel P *et al*. Bone mineral density and fracture prevalence in long-term kidney graft recipients. *Transplantation* 2002; **74**: 496–500.
9. Alem AM, Sherrard DJ, Gillen DL *et al*. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int*. 2000; **58**: 396–9.
10. Stehman-Breen CO, Sherrard DJ, Alem AM *et al*. Risk factors for hip fracture among patients with end-stage renal disease. *Kidney Int*. 2000; **58**: 2200–5.
11. Ball AM, Gillen DL, Sherrard D *et al*. Risk of hip fracture among dialysis and renal transplant recipients. *JAMA*. 2002; **288**: 3014–18.
12. Ramsey-Goldman R, Dunn JE, Dunlop DD *et al*. Increased risk of fracture in patients receiving solid organ transplants. *J. Bone Miner. Res*. 1999; **14**: 456–63.
13. Elder G, Mackun K. 25-Hydroxyvitamin D deficiency and diabetes predict reduced bone mineral density in patients with chronic kidney disease. *J. Bone Miner. Res*. 2006; **21**: 1778–84.
14. Jamal SA, Hayden JA, Beyene J. Low bone mineral density and fractures in long-term hemodialysis patients: A meta-analysis. *Am. J. Kidney Dis*. 2007; **49**: 674–81.
15. Vincenti F, Schena FP, Paraskevas S, Hauser IA, Walker RG, Grinyo J. A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. *Am. J. Transpl*. 2008; **8**: 307–16.
16. Farmer CKT, Hampson G, Abbs IC *et al*. Late low-dose steroid withdrawal in renal transplant recipients increases bone formation and bone mineral density. *Am. J. Transpl*. 2006; **6**: 2929–36.
17. Messa P, Sindici C, Cannella G *et al*. Persistent secondary hyperparathyroidism after renal transplantation. *Kidney Int*. 1998; **54**: 1704–13.
18. Akaberi S, Lindergard B, Simonsen O, Nyberg G. Impact of parathyroid hormone on bone density in long-term renal transplant patients with good graft function. Clin. *Transplantation* 2006; **82**: 749–52.
19. Cueto-Manzano A, Konel S, Hutchison AJ *et al*. Bone loss in long-term renal transplantation: Histopathology and densitometry analysis. *Kidney Int*. 1999; **55**: 2021–9.
20. Adachi JD, Ioannidis G, Berger C *et al*. The influence of osteoporotic fractures on health-related quality of life in community-dwelling men and women across Canada. *Osteoporos Int*. 2001; **12**: 903–8.
21. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B. Excess mortality after hospitalisation for vertebral fracture. *Osteoporos Int*. 2004; **15**: 108–12.
22. Nitsch D, Mylne A, Roderick P, Smeeth L, Hubbard R, Fletcher A. Chronic kidney disease and hip-fracture-related mortality in older people in the UK. *Nephrol Dial Transpl*. 2009; **24**: 1539–44.
23. Coco M, Rush H. Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. *Am. J. Kidney Dis*. 2000; **36**: 1115–21.
24. Abbott KC, Oglesby RJ, Hypolite IO *et al*. Hospitalizations for fractures after renal transplantation in the United States. *Ann. Epidemiol*. 2001; **11**: 450–57.
25. Lyles KW, Colon-Emeric CS, Magaziner JS *et al*. Zoledronic acid and clinical fracture and mortality after hip fracture. *N. Engl. J. Med*. 2007; **357**: 1799–809.
26. Jeffery JR, Leslie WD, Karpinski ME, Nickerson PW, Rush DN. Prevalence and treatment of decreased bone density in renal transplant recipients: A randomized prospective trial of calcitriol versus alendronate. *Transplantation* 2003; **76**: 1498–502.
27. Trabulus S, Altiparmak MR, Apaydin S, Serdengecti K, Sariyar M. Treatment of renal transplant recipients with low bone mineral density: A randomized prospective trial of alendronate, alfacalcidol, and alendronate combined with alfacalcidol. *Transpl. Proc*. 2008; **40**: 160–66.
28. Nayak B, Guleria S, Varma M *et al*. Effect of bisphosphonates on bone mineral density after renal transplantation as assessed by bone mineral densitometry. *Transpl. Proc*. 2007; **39**: 750–52.
29. Nowacka-Cieciura E, Cieciura T, Baczkowska T *et al*. Bisphosphonates are effective prophylactic of early bone loss after renal transplantation. *Transpl. Proc*. 2006; **38**: 165–7.
30. El-Agroudy AE, El-Husseini AA, El-Sayed M, Mohsen T, Ghoneim MA. A prospective randomized study for prevention of postrenal transplantation bone loss. *Kidney Int*. 2005; **67**: 2039–45.
31. Palmer SC, McGregor D, Strippoli G. Interventions for preventing bone disease in kidney transplant recipients (Review). *Cochrane Database of Syst. Rev*. 2007; **3**.
32. Miller P. Is there a role for bisphosphonates in chronic kidney disease? *Semin. Dial*. 2007; **20**: 186–90.
33. Mainra R, Elder G. Application of a treatment algorithm to avoid BMD loss and limit bisphosphonate use after kidney and kidney pancreas transplantation. *J. Bone Miner. Res*. 2008; **23**: SA497.