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ORIGINAL ARTICLE

Oral alendronate can suppress bone turnover but not fracture in kidney transplantation recipients with hyperparathyroidism and chronic kidney disease

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Abstract Post-transplantation bone diseases negatively affect the quality of life of solid organ recipients. Secondary or tertiary hyperparathyroidism is a frequent complication in kidney transplantation (KTx) recipients. Treatment with immunosuppressive agents including glucocorticoids can lead to deterioration in bone metabolism in these patients. In the present study, we explored the effects of a three-year treatment period with oral alendronate (ALN) in long-term KTx recipients. Post-KTx recipients were recruited ($n = 24$, M/F = 12/12, mean age 52.0 ± 7.8 years) into this study. All patients were prescribed methylprednisolone (4.07 ± 0.86 mg/day) with various immunosuppressive agents. Before treatment with oral ALN (35 mg/week), the mean concentrations of intact parathyroid hormone (iPTH) and 25-hydroxyvitamin D were 139.2 ± 71.4 pg/mL and 20.8 ± 4.1 ng/mL, respectively. After 36 months of ALN treatment, mean iPTH levels increased slightly (+20.9 %). Treatment with ALN reduced bone-specific alkaline phosphatase (−35.4 %), serum type I collagen N-terminal telopeptide (−31.2 %) and osteocalcin (−55.6 %) levels. ALN did not increase bone mass after 24 months. Four patients with the highest baseline iPTH levels suffered a clinical osteoporotic fracture during the 36-month ALN treatment period. Higher iPTH levels with chronic kidney disease (CKD) at baseline were associated with the incidence of new clinical fractures during ALN treatment. In conclusion, anti-resorptive therapy with ALN can suppress bone turnover even when iPTH concentration is elevated in long-term KTx recipients. However, hyperparathyroidism with CKD seems to be associated with new clinical fractures during ALN treatment.

Keywords Alendronate · Bone turnover · Kidney transplantation · Hyperparathyroidism

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Introduction

Advances in immunosuppressive therapy and transplant techniques have improved long-term organ-recipient survival [1]. Of solid organ transplantations, kidney transplantation (KTx) is currently a common and effective therapy in patients with end-stage renal disease (ESRD), and patients undergoing KTx can expect long-term graft and survival rates. Despite the benefits of KTx, this procedure can result in many disorders in ESRD patients, and osteoporosis remains a serious complication in KTx recipients [2]. The cumulative prevalence of osteoporotic fractures within 3 years of KTx is approximately 15 %, and the incidence of fractures in KTx recipients is three times higher than in dialysis patients [3–6]. After grafting, rapid bone loss was found during the first 6–18 months; however, long-term changes in bone mineralization depend on pre-existing chronic kidney disease-related mineral and

bone disorder (CKD-MBD) [7], and other clinical risk factors such as hyperparathyroidism and glucocorticoid therapy [6]. Accompanying the longer survival rate in KTx recipients, there is an increasing awareness of osteoporotic fracture as a chronic complication which can cause deterioration in the quality of life of KTx recipients.

Anti-resorptive therapy with bisphosphonates (BPs) is known to be one of the standard therapies for both primary and glucocorticoid-induced osteoporosis (GIOP) [8–11]. GIOP results in a high fracture risk and specific guidelines to treat GIOP have been launched in many countries including Japan [12–15]. Although BPs including alendronate (ALN) are considered the first-choice drugs for GIOP, information on the efficacy and safety of BPs in patients with GIOP after KTx is mostly limited to early bone loss after KTx [16–22]. In this work, we conducted a two-arm study. The first arm is a retrospective observational study to see the association between prevalent clinical fractures and their clinical characteristics. The second arm is a prospective observational study to see the efficacy and safety of oral ALN treatment in long-term KTx recipients.

Materials and methods

Subjects

Post-renal transplantation recipients were recruited into this study ($n = 24$, M/F = 12/12, mean age 52.0 ± 7.8 years) as shown in Table 1. The causes of chronic renal failure were 15 cases of chronic glomerular nephritis, 3 cases of immunoglobulin A nephropathy, 2 cases of pregnancy-induced hypertension, 1 case of lupus nephritis, and 3 unknown cases. The mean duration of hemodialysis and the duration of post-KTx were 7.4 ± 5.2 and 10.8 ± 3.4 years, respectively. Mean estimate glomerular filtration rate (eGFR) was 49.7 ± 17.8 mL/min/1.73 m^2, and eGFR in two-thirds of patients (18/24) were <60 mL/min/1.73 m^2, which is considered as CKD. All the subjects were prescribed methylprednisolone (4.07 ± 0.86 mg/day) and several immunosuppressants including cyclosporine (23/24), mizoribine (9/24), tacrolimus hydrate (1/24) and mycophenolate mofetil (4/24). Patients treated with BPs, estrogen, raloxifene, calcitonin and/or active vitamin D were excluded from this study. Thus, all patients were naive to anti-resorptive agents including BPs. Clinical fractures in this study were defined as non-traumatic low-energy fractures according to personal interviews with the patients and their medical records. No patients had clinical osteoporotic fractures before starting hemodialysis. However, a history of prevalent osteoporotic fractures after KTx was recorded as 9 clinical fractures in 7 subjects. The breakdown was 4 wrist fractures, 2 rib fractures, 1 leg fracture and 1 cuboidal fracture. Baseline data were collected from 24 patients who visited our hospital, agreed to participate in this study and whose biochemical parameters were recorded as a part of a routine follow-up for KTx recipients in October 2007.

Table 1 Details of study subjects

Number of subjects	24
Age (years)	52.0 ± 7.8
Gender (M/F)	12/12
Duration of hemodialysis (years)	7.4 ± 5.2
Duration after transplantation (years)	10.8 ± 3.4
Serum parameters	
eGFR (mL/min/1.73 m^2)	49.4 ± 17.8
Calcium (mg/dL)	9.8 ± 0.6
Phosphate (mg/dL)	3.0 ± 0.6
Intact PTH (pg/mL)	139.2 ± 71.4
1,25$(OH)_2$ vitamin D (pg/mL)	47.5 ± 16.0
25(OH) vitamin D (ng/mL)	20.8 ± 4.1
BAP (IU/L)	27.1 ± 8.1
NTx (nmol BCE/L)	16.9 ± 7.0
Osteocalcin (ng/mL)	11.3 ± 4.7
Immunosuppressive agents (mg/day)	
Methylprednisolone (24/24)	4.07 ± 0.86
Cyclosporin (23/24)	113 ± 33
Mizoribine (13/24)	158 ± 53
Tacrolimus hydrate (1/24)	3.0
Mycophenolate mofetil (5/24)	1125 ± 250
Clinical fracture before treatment	7/24

Each value represents mean ± SD

eGFR estimated glomerular filtration rate, *PTH* parathyroid hormone, *BAP* bone-specific alkaline phosphatase, *NTx* type I collagen N-terminal telopeptide

Oral ALN (5 mg daily or 35 mg weekly) was prescribed to all patients. Serum samples were collected at 0, 6, 12, 24 and 36 months. This study was approved by the Fujita Health University Review Board for Epidemiology and Clinical Studies (Aichi, Japan). It was therefore undertaken in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed written consent was obtained from each subject.

Measurements

Serum 25-hydroxyvitamin D (25-OHD) levels were measured with direct RIA (DiaSorin, Inc., Stillwater, MN, USA). Intact parathyroid hormone (iPTH) was measured with two-site IRMA (Nichols Diagnostics Institute., San Clemente, CA, USA). Serum type I collagen N-terminal telopeptide (NTx) and bone-specific alkaline phosphatase (BAP) were measured by ELISA (Osteomark NTx, Alere Inc.,Waltham, MA, USA) and by EIA (Osteolinks BAP,

DS Pharma Biomedical Co., Ltd., Osaka, Japan), respectively. Reference ranges of NTx and BAP to evaluate the risk of osteoporotic fracture were defined according to the guidelines for the use of biochemical markers for bone turnover in osteoporosis [23]. Serum osteocalcin was measured by IRMA (BGP IRMA Mitsubishi, Mitsubishi Chemical Medience Co., Tokyo, Japan). Routine chemistries were measured using an Olympus AU5232 automatic analyzer (Olympus Co., Tokyo, Japan). When the serum albumin level was <4.0 mg/dL, serum calcium concentration was corrected by the method of Payne et al. [24]. eGFR was calculated by the method of Matsuo et al. [25]. Bone mineral density (BMD) at the lumbar spine (L2–4) was assessed by dual X-ray absorptiometry (Discovery, Hologic Inc., Bedford, MA, USA) at 0, 12 and 24 months of ALN treatment.

Statistical analysis

All analyses were performed with using the statistical software JMP 8.0.1 (SAS Inc, Cary, NC, USA). Continuous variables were analyzed using an unpaired Student's *t* test. If data were not normally distributed, Wilcoxon nonparametric test was used. Relationship between bone turnover markers were examined using single regression analysis. For analysis of the effect of ALN on bone turnover markers in each subject, the data were analyzed using univariate regression analysis and Wilcoxon nonparametric test. $P < 0.05$ was considered significant.

Results

Before treatment with oral ALN, the mean concentrations of iPTH and 25-OHD were 139.2 ± 71.4 pg/mL and 20.8 ± 4.1 ng/mL, respectively (Table 1). Although eGFR was slightly low, serum Ca, Pi and 1,25-dihydroxy vitamin D [1,25$(OH)_2$D] concentrations remained within normal limits. Mean serum NTx level (16.9 ± 7.0 nmol BCE/L) was high, and 11 patients had serum NTx levels above the reference range (7.5–16.5 nmol BCE/L). Mean BAP level (27.1 ± 8.1 IU/L) was also high and 11 patients had levels above the reference range (reference range for premenopausal women 7.9–29.0 U/L). In contrast, mean osteocalcin level was 11.3 ± 4.7 ng/mL (reference range 2.5–13 ng/mL), and only 3 of 24 subjects had levels above the reference range. Serum iPTH level was positively associated with serum osteocalcin level ($R = 0.44$, $P = 0.030$, $n = 24$), but not with 25-OHD, NTx or BAP concentration at baseline (data not shown).

Treatment with ALN significantly increased serum iPTH levels at 6, 12, and 24 months (Table 2). Mean iPTH level at 36 months was still about 1.2 times higher than that at baseline, although not statistically significant. In contrast, 25-OHD concentrations were unaffected during the treatment period. Treatment with ALN significantly reduced serum BAP (−35.4 %), NTx (−31.2 %) and osteocalcin (−55.6 %) levels from 6 to 36 months (Table 2); however, ALN did not affect serum Ca, P or eGFR levels (Table 2). Mean lumbar BMD before treatment was 0.80 ± 0.11 g/cm^2. After ALN treatment, BMD levels were not significantly changed at 12 months (+0.04 ± 2.84 %) or 24 months (+0.09 ± 3.23 %) (Table 2).

Seven patients had a history of clinical fractures after KTx at baseline. There were no differences in serum iPTH, BAP, NTx, osteocalcin, Ca, Pi, BMD or eGFR levels between the patients with prevalent clinical fractures and those without fractures (data not shown). There were 5 clinical fractures in 4 patients (M/F = 2/2) during the

Table 2 Change of lumbar BMD and laboratory data before and after the treatment

	Pre	6 months	12 months	24 months	36 months
BMD (L2–4) (g/cm^2)	0.80 ± 0.11	–	0.78 ± 0.12	0.79 ± 0.15	–
Intact PTH (pg/mL)	139 ± 71	179 ± 116*	191 ± 149*	188 ± 122*	168 ± 129
25(OH) VD (ng/mL)	20.8 ± 4.1	–	20.4 ± 5.6	20.7 ± 5.7	23.4 ± 8.4
1,25$(OH)_2$ VD (pg/mL)	47.5 ± 16.0	46.7 ± 15.0	46.4 ± 15.5	47.8 ± 17.8	51.2 ± 12.4
BAP (IU/L)	27.1 ± 8.1	24.0 ± 9.2*	19.4 ± 7.1*	17.5 ± 5.6*	18.8 ± 9.4*
Osteocalcin (ng/mL)	11.3 ± 4.7	7.7 ± 4.1*	6.6 ± 3.2*	5.7 ± 2.9*	5.0 ± 2.7*
Serum NTx (nmol BCE/L)	16.9 ± 5.7	12.9 ± 5.7*	12.4 ± 5.4*	13.2 ± 5.4*	11.7 ± 5.3*
eGFR (mL/min/1.73 m^2)	49.4 ± 17.8	49.1 ± 19.6	46.9 ± 17.4	49.1 ± 19.6	46.9 ± 17.4
Calcium (mg/dL)	9.8 ± 0.6	9.9 ± 0.5	10.0 ± 0.5	9.8 ± 0.6	10.0 ± 0.6
Phosphate (mg/dL)	3.0 ± 0.6	2.9 ± 0.5	2.9 ± 0.5	3.0 ± 0.5	3.0 ± 0.4

Each value represents mean ± SD

BMD bone mineral density, *PTH* parathyroid hormone, *VD* vitamin D, *BAP* bone-specific alkaline phosphatase, *NTx* type I collagen N-terminal telopeptide, *eGFR* estimated glomerular filtration rate

* $P < 0.05$ versus pre-treatment

Table 3 Association between new clinical fracture and the change of bone turnover markers during oral alendronate treatment

	Fracture (−) ($n = 20$)	Fracture (+) ($n = 4$)	*P* value	Odds ratio (95 %CI)
Intact PTH (pg/mL)				
Before	116.0 ± 52.6	255.0 ± 3.0	<0.0001	–*
6 months	149.4 ± 78.7	327.5 ± 167.3	0.064	1.017 (0.999–1.034)
% change at 6 months	29.8 ± 40.7	28.0 ± 63.9	0.936	0.999 (0.974–1.025)
Serum NTx (nmol BCE/L)				
Before	16.3 ± 5.3	20.4 ± 3.6	0.199	1.142 (0.933–1.340)
6 months	12.6 ± 6.2	14.3 ± 1.77	0.566	1.054 (0.881–1.260)
% change at 6 months	−23.3 ± 21.4	−19.3 ± 40.8	0.763	1.007 (0.964–1.051)
Serum BAP (IU/L)				
Before	26.1 ± 7.4	32.3 ± 10.6	0.174	1.112 (0.954–1.300)
6 months	23.3 ± 9.6	27.5 ± 6.62	0.397	1.052 (0.936–1.182)
% change at 6 months	−12.4 ± 17.5	−9.5 ± 25.2	0.770	1.009 (0.949–1.073)
Serum OC (ng/mL)				
Before	10.6 ± 4.0	14.8 ± 3.6	0.119	1.233 (0.947–1.606)
6 months	7.30 ± 4.34	9.53 ± 1.95	0.327	1.132 (0.884–1.450)
% change at 6 months	−20.2 ± 69.3	−29.1 ± 34.9	0.800	0.997 (0.976–1.19)
25(OH) D (ng/mL)				
Before	20.3 ± 4.2	23.8 ± 2.4	0.144	1.248 (0.927–1.682)
12 months	20.5 ± 5.8	20.3 ± 5.7	0.947	0.993 (0.816–1.210)
% change at 12 months	1.14 ± 20.8	−15.4 ± 17.7	0.165	0.955 (0.895–1.019)
eGFR (mL/min/1.73 m^2)				
Before	51.8 ± 17.5	37.0 ± 15.8	0.157	0.934 (0.850–1.026)
6 months	50.8 ± 19.3	40.7 ± 21.3	0.350	0.966 (0.905–1.032)
% change at 6 months	−2.8 ± 21.6	6.2 ± 12.8	0.184	1.087 (0.961–1.230)

Each data represents mean ± SD. Data were analyzed by univariate logistic regression test

PTH parathyroid hormone, *BAP* bone-specific alkaline phosphatase, *NTx* type I collagen N-terminal telopeptide, *OC* osteocalcin, *25(OH)D* 25-hydroxyvitamin D, *eGFR* estimated glomerular filtration rate

* $P < 0.001$: odds ratio and its 95 % CI were not available because iPTH level at baseline completely predicted new clinical fracture as an explanatory variable

3-year ALN treatment period. The breakdown was 2 leg fractures, 1 vertebral fracture (lumbar spine), 1 hip fracture and 1 humeral fracture. The patients who had clinical fractures during ALN treatment had higher iPTH levels at baseline with ALN treatment (Table 3). Indeed, all 4 patients with a high baseline iPTH level (≥240 pg/ml) had new clinical fractures whereas others (iPTH < 240 pg/ml) had no new fracture. Other bone turnover markers such as BAP, NTx and osteocalcin at baseline and at 6 months with ALN treatment were not related to new clinical fractures. When we divided patients into 4 groups according to iPTH levels at baseline (quartile 1–4), all the patients with new clinical fracture belonged to the highest iPTH quartile (Q4) group, while the number of prevalent fractures increased according to the elevation of the iPTH level (Table 4). Although eGFR in Q4 was lower than Q1, univariate regression analysis revealed that not eGFR but iPTH level at baseline was an independent risk factor for new clinical fracture. There were no serious adverse effects due to ALN treatment, and the adherence of ALN in this study was between 80 and 100 %.

Discussion

After KTx, there are at least three major risk factors for osteoporosis in these patients—(1) persistent hyperparathyroidism, (2) glucocorticoids, and (3) calcineurin inhibitors [6]. Some KTx recipients still have high bone turnover [5], and bone loss is greater in KTx recipients with elevated biochemical markers of bone turnover [26]. In the present study, we found that hyperparathyroidism with PTH resistance continued in long-term KTx recipients. Serum iPTH level was not associated with prevalent fractures at baseline, but did predict new clinical fractures even under ALN treatment. ALN increased iPTH levels throughout

Table 4 Association between serum intact parathyroid hormone (iPTH) level and the incidence of clinical fracture according to iPTH quartile at baseline ($n = 24$)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Gender (M:F)	1:5	3:3	3:3	4:2
Age (years)	52.7 ± 5.0	51.2 ± 7.4	48.7 ± 7.8	55.7 ± 10.3
Duration of hemodialysis (years)	6.0 ± 5.2	5.5 ± 2.2	9.3 ± 5.3	8.5 ± 6.6
Duration after transplantation (years)	13.3 ± 4.1	9.7 ± 3.8	11.2 ± 2.8	9.3 ± 2.7
Dose of MPSL (mg)	3.5 ± 0.8	4.0 ± 0.0	4.0 ± 0.0	4.3 ± 2.0
Intact PTH (pg/mL)	61.1 ± 15.3	98.0 ± 6.8*	160 ± 28.9*	238 ± 27.5*
25(OH)D (ng/mL)	24.0 ± 4.5	18.1 ± 3.1*	18.5 ± 2.7*	22.8 ± 3.0
Serum NTx (nmol BCE/L)	13.9 ± 4.3	17.8 ± 7.0	17.0 ± 4.7	19.1 ± 6.5
Serum BAP (IU/L)	26.0 ± 5.6	25.0 ± 7.3	25.6 ± 7.7	31.9 ± 10.8
Serum OC (ng/mL)	8.0 ± 1.2	11.1 ± 7.5*	12.7 ± 2.6*	13.3 ± 4.0*
eGFR (mL/min/1.73 m^2)	58.6 ± 18.6	48.2 ± 21.7	53.5 ± 13.4	37.1 ± 12.5*
BMD (L2–4) (g/cm^2)	0.81 ± 0.10	0.85 ± 0.12	0.69 ± 0.03	0.80 ± 0.13
% change of BMD at 12 M	2.34 ± 0.41	−3.30 ± 2.05	−0.68 ± 4.62	−1.90 ± 1.43
Prevalent fracture	0	3	1	5
New fracture during alendronate treatment	0	0	0	5

The range of iPTH was as follows: first quartile, <84 pg/mL; second quartile, 85–111 pg/mL; third quartile, 112–194 pg/mL; and fourth quartile, >194 pg/mL

Each value represents mean ± SD

MPSL methylprednisolone, *PTH* parathyroid hormone, *25(OH)D* 25-hydroxyvitamin D, *NTx* type I collagen N-terminal telopeptide, *BAP* bone-specific alkaline phosphatase, *OC* osteocalcin, *eGFR* estimated glomerular filtration rate, *BMD* bone mineral density

* $P < 0.05$ versus quartile 1 by Wilcoxon nonparametric test

this study, and secondary hyperparathyroidism has been reported to increase vertebral fracture [27]. Although two-thirds of our patients had CKD, which strongly affected bone metabolism, iPTH level at baseline was independently associated with new clinical fracture during the treatment. These findings suggest the need for strategies aimed at lowering serum PTH in KTx recipients.

All of the study subjects received glucocorticoids, and 23 of 24 patients received calcineurin inhibitors, which also increased the risk of osteoporotic fracture. BPs are widely used in the treatment of primary osteoporosis and GIOP, and their efficacy in preventing osteoporotic fractures has been established [8–11]. Due to the lack of relevant clinical data on the efficacy and safety of BPs in patients with severe renal impairment, oral BPs carry a governmental registration warning regarding their use in patients with low creatinine clearance such as <30 mL/min [28]. In order to avoid the risk of damaging kidney function, research on the efficacy and safety of BPs in KTx recipients is mostly limited to early bone loss after KTx [16–22]. Here we showed that ALN treatment in long-term (10.8 ± 3.4 years) KTx recipients did not affect eGFR or induce no serious adverse effects.

In the present study, we showed that ALN did not increase BMD at the lumbar spine even when ALN significantly reduced bone turnover markers. There are several possibilities as to why ALN failed to increase BMD at the lumbar spine. Firstly, the presence of hyperparathyroidism during our study diminished the effect of ALN. Almonde et al. [29] reported that the decrease in vertebral bone mass in female KTx recipients was related to the elevation in PTH, while a decrease in femoral neck BMD in male recipients was observed in subjects with low PTH. Secondly, the effect of ALN might be site-specific. In some previous reports, ALN effectively increased lumbar BMD in KTx patients [16–21]; however, another report showed that ALN increased femoral BMD but not lumbar BMD after KTx [30]. Thirdly, the lack of vitamin D supplementation might have affected the efficacy of ALN, because ALN itself increased iPTH levels in our patients. We have previously shown a high prevalence of vitamin D deficiency in both the normal population and in diabetic patients in Japan [31, 32], and found that 25-OHD levels in 11 of 24 patients was <20 ng/mL in this study. However, we often hesitate to treat patients with renal impairment with vitamin D in order to avoid the risk of inducing hypercalcemia, hypercalciuria and renal calcification. As alfacalcidol has been reported to reduce bone loss in KTx patients [20, 33], active vitamin D could be beneficial in KTx recipients to stratify the efficacy of anti-resorptive agents. Further studies would be required.

There were several limitations in this study. Firstly, this study did not include control patients such as a placebo group due to the moderately high risk of fracture.

Secondly, the number of subjects was too small to evaluate the efficacy of the bone resorptive agent on osteoporotic clinical fractures especially for hip fracture. Thirdly, we examined only lumbar BMD, which might be affected by aortic calcification. Fourthly, serum NTx level could be affected by kidney function. Fifthly, we cannot adapt logistic regression analysis, because iPTH level at baseline completely predicted new clinical fracture as an explanatory variable. Sixthly, this study was conducted at only one center.

In conclusion, anti-resorptive therapy with ALN can suppress bone turnover even when iPTH concentration is elevated in long-term KTx recipients. However, hyperparathyroidism with CKD seems to be associated with new clinical fractures during ALN treatment.

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Conflict of interest All authors have no conflict of interest.

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