# Effect of Ibandronate on Bone Loss and Renal Function after Kidney Transplantation

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*Abstract.* Severe osteoporosis frequently is observed after organ transplantation. In kidney transplantation, it adds to preexisting renal bone disease and strategies to prevent osteoporosis are not established. Eighty kidney recipients were included in a randomized controlled prospective intervention trial. Treated patients ($n = 40$) received an injection of ibandronate, a bisphosphonate, immediately before and at 3, 6, and 9 mo after transplantation. The primary outcome measured was the change in bone mineral density. Secondary measures included graft outcome, spinal deformities, fracture rate, body height, and hormonal and metabolic data. Loss of spongy and cortical bone after transplantation was prevented by ibandronate. Changes of bone mineral density (ibandronate *versus* controls) were as follows: lumbar spine, $-0.9 \pm 6.1\%$ *versus* $-6.5 \pm 5.4\%$ ($P < 0.0001$); femoral neck, $+0.5 \pm 5.2\%$ *versus* $-7.7 \pm 6.5\%$ ($P < 0.0001$); and midfemoral shaft, $+2.7 \pm 12.2\%$ *versus* $-4.0 \pm 10.9\%$ ($P = 0.024$). Fewer spinal deformities developed with ibandronate (7 patients with 7 deformities *versus* 12 patients with 23 deformities; $P = 0.047$). Loss of body height was $0.5 \pm 1.0$ cm *versus* $1.1 \pm 1.0$ cm in control subjects ($P = 0.040$). Two bone fractures occurred in each group. There were fewer acute rejection episodes with ibandronate (11 *versus* 22; $P = 0.009$). Graft function after 1 yr was comparable. Bone loss, spinal deformation, and loss of body height during the first year after kidney transplantation are prevented by injection of ibandronate at intervals of 3 mo. The smaller number of rejection episodes of the ibandronate-treated group should be confirmed and its mechanism should be explored in additional studies.

Osteoporosis is a systemic bone disease characterized by altered bone architecture, reduced bone mass, and increased fracture rate (1). Osteoporosis occurs after heart (2), liver (3), kidney (4), and bone marrow transplantation (5), in both genders. A decrease of bone mineral density below 2 SD is reported in 28 to 73% (6,7) and fractures in 11 to 38% (3,8) of all graft recipients. Several risk factors contribute to a rapid loss of bone mineral density within the first few months after transplantation: corticosteroids, cyclosporine, immobilization, hypogonadism, and hyperparathyroidism (2,8,9). Loss of bone mineral density ranging between 1 and 3% per year is prevented by bisphosphonates in corticosteroid-induced osteoporosis (10,11). Although posttransplantation osteoporosis is more severe and has a more complex pathogenesis, treatment with bisphosphonates may be promising. It is unclear whether these drugs interfere with graft outcome. To determine the effects of prophylactic intermittent therapy with ibandronate on posttransplantation osteoporosis and graft outcome, we performed a 12-mo randomized, controlled study of renal allograft recipients.

## Materials and Methods

### *Patients*

Male and female patients who were awaiting kidney transplantation at the University Hospital of Freiburg (20 to 60 yr of age) gave informed consent. The study protocol was approved by the local ethics committee. Patients with combined kidney and pancreas grafts were excluded.

### *Study Design*

Eighty of 114 consecutive renal allograft recipients were randomized to treatment or control (Figure 1). Patients had diet counseling to achieve an intake of at least 1000 mg of calcium per day. Patients with intolerance to dairy products were supplemented with 500 mg of calcium (Calcium-Sandoz forte, Basel, Switzerland). Treated patients received four intravenous bolus injections of ibandronate (Bondronat, Roche, Weil am Rhein, Germany). Dosages were 1 mg immediately before and 2 mg at 3, 6, and 9 mo after transplantation. The dosing schedule is based on a previous study that investigated the effect of different doses of ibandronate in postmenopausal osteoporosis (12). The dose before transplantation was reduced to account for renal insufficiency. The primary end point was the change of bone mineral

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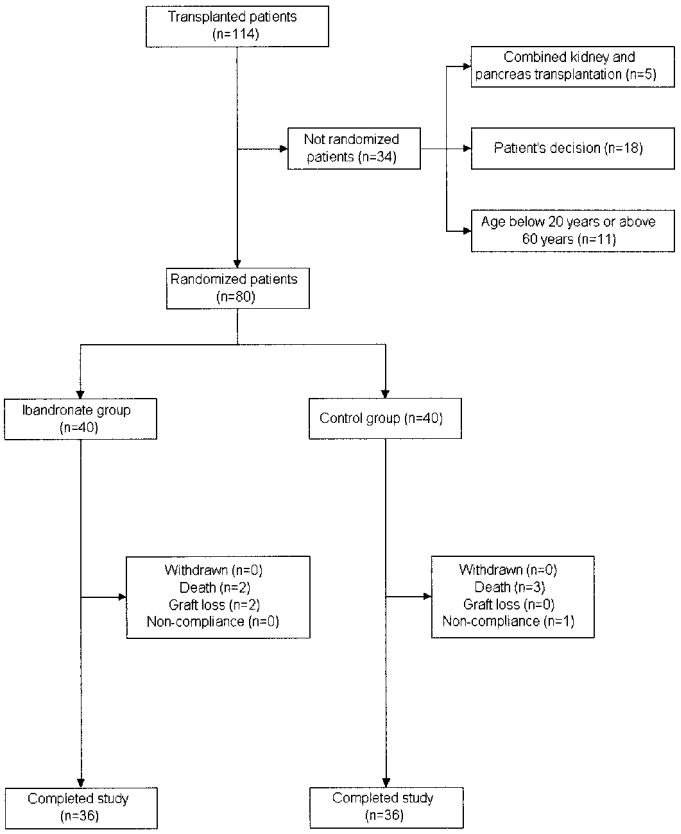


*Figure 1.* Patient randomization.

density after 12 mo. Graft outcome, spinal deformities, fractures, body height, and hormonal and metabolic data also were recorded.

### *Bone Mineral Density Measurement*

Bone mineral density was measured by dual energy x-ray absorptiometry (DEXA-L Lunar) at lumbar spine (L1 to L4; spongy bone), femoral neck (spongy and cortical bone), and midfemoral shaft (cortical bone) because of its different admixture of cortical and trabecular bone. Results are expressed as absolute values in gram hydroxylapatite per square centimeter ($g/cm^2$) and as relative values in number of SD below the expected normal gender-, age-, and weight-adjusted bone mineral density value. Calibration was performed daily. The precision error was 0.011 $g/cm^2$. A standard set of lateral radiographs was obtained to select radiographically intact lumbar vertebrae. The average bone mineral density of vertebrae L2 to L4 was calculated.

### *Radiologic Measurements*

At the end of the study, all x-rays were evaluated by a radiologist who was blinded to the randomization. Anterior and posterior height of each lumbar vertebra (L1 to L5) was measured. A new (incident) vertebral deformity was defined as reduction of the sum of anterior and posterior height of each lumbar vertebra greater than 5% between the baseline and follow-up radiographs (13). A vertebral fracture was defined as reduction of the anterior or posterior height greater than 20% compared with the adjacent vertebrae. Body height was measured in the morning at the same time for each patient.

### *Laboratory Measurements*

Serum creatinine, alkaline phosphatase, serum phosphate, and serum calcium were assayed with routine methods. Prolactin, follicle-stimulating hormone, luteinizing hormone, and estradiol were measured by immunoradiometric magnetic solid phase assays (MAIAclone; Biochem Immunosystems, Freiburg, Germany). Free testosterone and DHEA-SO4 were measured by coated tube assays (coat a count; DPC, Los Angeles, CA). Plasma intact parathyroid hormone was determined by immunoradiometric assay (Allegro; Nichols Institute, Bad Nauheim, Germany), 25-hydroxycholecalciferol was measured by radioimmunometric assay (25(OH)-vitamin D RIA, IBL, Hamburg, Germany), 1,25-hydroxycholecalciferol was measured by radio receptor assay ($1,25(OH)_2$-vitamin D radioreceptor assay; Immundiagnostik, Bensheim, Germany), bone alkaline phosphatase was determined by immunoradiometric assay (Ostase; Beckmann, München, Germany), osteocalcin was measured by enzyme-linked immunosorbent assay (Osteocalcin; IBL, Hamburg, Germany), and pyridinoline and deoxypyridinoline were measured by HPLC after acid hydrolysis of the urine samples (Pyridinium-Crosslinks; Biorad, München, Germany). Normal values are provided in Table 1.

### *Comedication and Immunosuppressive Therapy*

Patients with initial vitamin D deficiency below 15 ng/ml were supplemented with a single dose of 10,000 U of cholecalciferol (11 patients in the ibandronate and 8 patients in the control group; vitamin D levels are shown in Table 1). Hormone replacement therapy was continued (one postmenopausal woman in each group). Immunosuppressive therapy consisted of cyclosporine dosed to a blood level of 120 to 180 ng/ml; prednisone 100 mg for 5 d, 50 mg for 5 d, 25 mg for 10 d, and tapered to 5 mg after 1 yr; and mycophenolate mofetil 2 g/d. Patients who were receiving kidneys from unrelated living donors were treated additionally with antilymphocyte globulin for 10 d. Acute rejections were treated with three boluses of 500 mg of prednisone. Refractory cases received a 10-d course of antilymphocyte globulin.

### *Acute Rejections*

Acute rejections were clinically suspected when one or more of the following criteria were present: increase in size and/or decrease in tenderness of the graft and increase in serum creatinine and/or decrease in urine volume after exclusion of other reasons (14). Clinically suspected rejections were confirmed by biopsy (Department of Pathology, University Freiburg). When a biopsy was not possible, patients were considered to have acute rejection when there was a positive response to prednisone bolus therapy (decrease in serum creatinine and increase in urine volume).

### *Statistical Analyses*

Sample sizes were calculated for an assumed 5% difference in bone mineral density, an SD of 7.5, a power of 80%, and a two-sided level of significance of 0.05, assuming a 10% loss of patients. The $\chi^2$ test was used for qualitative variables, and the Mann-Whitney *U* test was used for quantitative variables. ANOVA for repeated measurements was used for the investigation of bone mineral density values using treatment groups as covariate. Dropouts were not included in the analysis. Missing values were not substituted. The impact of metabolic parameters on the treatment effect was studied by introducing the corresponding covariate and by analysis of the ANOVA interaction term. Multivariate analysis was performed with stepwise backward elimination procedure. Results are presented as means ± SD.

## Results

Seventy-two of 80 randomized patients completed the 12-mo study. At baseline, patient characteristics (Table 2),

*Table 1.* Metabolic parameters at baseline and after 6 and 12 mo[a]

| Parameter | Normal Values | Ibandronate Group | | | Control Group | | |
|---|---|---|---|---|---|---|---|
| | | Baseline | 6 Mo | 12 Mo | Baseline | 6 Mo | 12 Mo |
| Serum calcium (mmol/L) | 2.15–2.75 | 2.49 ± 0.23 | 2.58 ± 0.16 | 2.58 ± 0.19[c] | 2.48 ± 0.21 | 2.52 ± 0.25 | 2.53 ± 0.18 |
| Serum phosphate (mmol/L) | 0.81–1.61 | 1.88 ± 0.59 | 0.95 ± 0.24 | 0.99 ± 0.24[d] | 1.93 ± 0.61 | 1.04 ± 0.28 | 1.03 ± 0.25[e] |
| Alkaline phosphatase (U/L) | 40–200 | 109 ± 56 | 189 ± 140 | 156 ± 81[e] | 126 ± 72 | 164 ± 91 | 172 ± 88[c] |
| Bone alkaline phosphatase (U/L) | 15–41 | 17 ± 9 | 36 ± 35 | 31 ± 20[e] | 23 ± 19 | 31 ± 20 | 35 ± 24[b] |
| Osteocalcin ($\mu$g/L) | 3–8 | 31 ± 27 | 13 ± 8 | 10 ± 6[e] | 31 ± 21 | 13 ± 6 | 11 ± 6[e] |
| 25-OH-cholecalciferol (ng/ml) | 20–120 | 36 ± 35 | 25 ± 14 | 36 ± 20[b] | 35 ± 35 | 28 ± 24 | 28 ± 15 |
| 1,25-OH-cholecalciferol (pg/ml) | 17–53 | 12 ± 12 | 31 ± 14 | 42 ± 20[e] | 11 ± 11 | 31 ± 16 | 43 ± 20[e] |
| Parathyroid hormone (pg/ml) | 10–55 | 200 ± 177 | 66 ± 46 | 65 ± 42[e] | 232 ± 258 | 94 ± 139 | 90 ± 87[d] |
| Serum creatinine ($\mu$mol/l) | 44–97 | 874 ± 295 | 110 ± 36 | 115 ± 40[d] | 809 ± 179 | 129 ± 60 | 142 ± 100[e] |
| Prolactin ($\mu$E/ml) | <540 | 1020 ± 1447 | 238 ± 86 | 291 ± 253[d] | 540 ± 473 | 227 ± 85 | 239 ± 129[d] |
| Follicle-stimulating hormone (mE/ml) | <10 | 26 ± 47 | 17 ± 24 | 15 ± 28[b] | 17 ± 40 | 12 ± 21 | 12 ± 22 |
| Luteinizing hormone (mE/ml) | <10 | 19 ± 27 | 10 ± 16 | 8 ± 15[d] | 13 ± 21 | 6 ± 10[b] | 7 ± 10[b] |
| Estradiol (pg/ml) | 10–240 | 54 ± 38 | 39 ± 50 | 39 ± 50 | 64 ± 62 | 43 ± 48 | 57 ± 103 |
| Testosterone (pg/ml) | 0.7–47 | 13 ± 10 | 11 ± 9 | 11 ± 8 | 13 ± 11 | 12 ± 9 | 11 ± 8 |
| Dihydroepiandrosterone (ng/ml) | 350–5600 | 2319 ± 2090 | 644 ± 384 | 669 ± 488[e] | 2000 ± 1972 | 620 ± 274 | 543 ± 284[e] |
| Pyridinoline (nmol/mmol creatinine) | 40–100 | 90 ± 36[f] | 157 ± 307 | 85 ± 55 | 106 ± 57[f] | 83 ± 39 | 79 ± 48[c] |
| Deoxypyridinoline (nmol/mmol creatinine) | 9–20 | 48 ± 141[f] | 24 ± 29 | 18 ± 15 | 32 ± 31[f] | 16 ± 14 | 17 ± 11[c] |

[a] There were no significant differences between groups at baseline and during follow-up (*t* test for unpaired values) except for luteinizing hormone in ANOVA for repeated measurements, $P < 0.05$.
[b] Difference during time within group, $P < 0.05$ (ANOVA for repeated measurements).
[c] Difference during time within group, $P < 0.01$ (ANOVA for repeated measurements).
[d] Difference during time within group, $P < 0.001$ (ANOVA for repeated measurements).
[e] Difference during time within group, $P < 0.0001$ (ANOVA for repeated measurements).
[f] Urine values were obtained 3 wk after transplantation.

bone mineral density (Table 3), and biochemical markers (Table 1) did not differ between treatment and control groups. Three patients on ibandronate and four control subjects had a single crushed vertebra at study entry. The immunosuppressive protocol was the same for both groups (Table 4).

### *Bone Measurements*

Progression of osteoporosis after transplantation was prevented by ibandronate (lumbar spine, −0.9 ± 6.1% from baseline; femoral neck, +0.5 ± 5.2%; and midfemoral shaft, +2.7 ± 12.2%). In control subjects, the greatest bone loss occurred during the first 6 mo. After 1 yr, bone mineral density of control subjects had decreased at lumbar spine (−6.5 ± 5.4% from baseline), femoral neck (−7.7 ± 6.5%), and midfemoral shaft (−4.0 ± 10.9%). Ibandronate-treated patients and control subjects differed significantly (lumbar spine, $P < 0.0001$; femoral neck, $P < 0.0001$; midfemoral shaft, $P = 0.024$ [ANOVA]; Figure 2).

Subgroup analysis was done for antirejection therapy, gender, menopause, age, level of parathyroid hormone, and vitamin D supplementation. Patients with rejection had a significantly higher cumulative dose of prednisone as compared with patients without rejections (7362 ± 903 mg *versus* 5920 ± 999 mg). Patients with rejection demonstrated significant benefit when treated with ibandronate ($n = 11$) as compared with control subjects ($n = 22$) at the femoral neck (−1.1 ± 6.9% *versus* −8.6 ± 6.1%; $P = 0.0025$; Figure 3). Similar changes were seen at the two other sites; however, differences did not approach significance (lumbar spine, −1.7 ± 8.1% *versus* −5.7 ± 4.9% [$P = 0.118$]; midfemoral shaft, +0.8 ± 15.1% *versus* −7.2 ± 11.3% [$P = 0.251$]). A similar benefit of ibandronate treatment was observed in patients without rejection (lumbar spine, −0.5 ± 5.2% *versus* −7.8 ± 6.0% [$P = 0.0002$]; femoral neck, +1.3 ± 4.4% *versus* −6.3 ± 7.0% [$P = 0.0002$]; midfemoral shaft, +3.5 ± 10.8% *versus* +1.0 ± 8.4% [$P = 0.204$]). Ibandronate protected bone loss in all other subgroups and measured sites except lumbar spine of post-

*Table 2.* Patient data at study entry

| Data | Ibandronate Group | Control Group |
|---|---|---|
| Number of patients | 36 | 36 |
| Men/women | 25/11 | 23/13 |
| Menopause | 5 | 6 |
| Time after menopause (yr)[a] | 5.3 ± 3.3 | 9.2 ± 6.1 |
| Diabetes mellitus | 1 | 1 |
| Age (yr)[a] | 42 ± 10 | 44 ± 10 |
| Time on dialysis (yr)[a] | 4.8 ± 3.4 | 4.7 ± 3.5 |
| Living donor | 14 | 13 |
| Cadaver donor | 22 | 23 |
| Number of mismatches[a] | | |
| A locus | 0.9 ± 0.7 | 0.9 ± 0.7 |
| B locus | 0.9 ± 0.7 | 1.2 ± 0.7 |
| DR locus | 0.8 ± 0.7 | 1.0 ± 0.7 |

[a] Mean ± SD. There were no significant differences.

*Table 3.* Bone mineral density at baseline and after 6 and 12 mo[a]

| Bone Mineral Density | Ibandronate Group | | | Control Group | | |
|---|---|---|---|---|---|---|
| | Baseline | 6 Mo | 12 Mo | Baseline | 6 Mo | 12 Mo |
| At lumbar spine (g/cm$^2$) | 1.137 ± 0.168 | 1.108 ± 0.169 | 1.126 ± 0.168[b] | 1.147 ± 0.166 | 1.078 ± 0.170 | 1.073 ± 0.166[d] |
| no. of SD below normal bone mineral density | −0.472 ± 1.416 | −0.778 ± 1.368 | −0.650 ± 1.294[c] | −0.369 ± 1.330 | −1.053 ± 1.421 | −1.142 ± 1.403[d] |
| At femoral neck (g/cm$^2$) | 0.860 ± 0.160 | 0.841 ± 0.155 | 0.864 ± 0.166[c] | 0.900 ± 0.140 | 0.827 ± 0.116 | 0.829 ± 0.125[d] |
| no. of SD below normal bone mineral density | −0.743 ± 1.227 | −0.986 ± 1.096 | −0.803 ± 1.148 | −0.388 ± 1.052 | −1.032 ± 0.900 | −1.071 ± 0.978[d] |
| At midfemoral shaft (g/cm$^2$) | 1.673 ± 0.382 | 1.729 ± 0.444 | 1.720 ± 0.434 | 1.720 ± 0.391 | 1.694 ± 0.402 | 1.641 ± 0.378 |

[a] Mean ± SD. There were no significant differences of baseline bone mineral density.
[b] Difference during time within group, $P < 0.05$.
[c] Difference during time within group, $P < 0.01$.
[d] Difference during time within group, $P < 0.0001$.

*Table 4.* Immunosuppressive therapy

| Therapy | Ibandronate Group | Control Group |
|---|---|---|
| Cumulative prednisone dosage (mg)[a] | | |
| 6 mo | 4604 ± 898 | 5087 ± 1144 |
| 12 mo | 6299 ± 1057 | 6863 ± 1269 |
| Prednisone dosage (mg/d)[a] | | |
| 6 mo | 13.1 ± 3.6 | 12.4 ± 3.8 |
| 12 mo | 8.2 ± 4.4 | 7.6 ± 2.9 |
| Cyclosporine trough level (ng/ml)[a] | | |
| 6 mo | 169 ± 56 | 189 ± 50 |
| 12 mo | 150 ± 28 | 146 ± 30 |
| Antirejection therapy | | |
| no. of patients[b] | 11 (31%) | 22 (61%) |
| steroid-resistant rejection | 4 (11%) | 5 (14%) |

[a] Mean ± SD. There were no significant differences except for the number of patients who received antirejection therapy.
[b] $P = 0.009$ by $\chi^2$.

menopausal women ($n = 5$). Furthermore, ibandronate was the strongest predictor of bone loss at lumbar spine ($P < 0.0001$) and femoral neck ($P < 0.0001$) in multivariate analysis using all hormonal metabolic data before transplantation and graft function at the end of the study. Especially parathyroid hormone value or serum creatinine did not influence the results. Twenty-five patients (ibandronate, $n = 13$; control subjects, $n = 12$) were followed for a second year. Without further osteoporosis treatment, bone mineral density remained stable or increased slightly in both groups.

Spinal deformities developed less frequently in the ibandronate group (7 patients with 7 deformities *versus* 12 patients with 23 deformities; $P = 0.047$ for deformities). On ibandronate, fewer patients lost body height (12 *versus* 21; $P = 0.033$). Mean height loss was 0.5 ± 1.0 cm *versus* 1.1 ± 1.0 cm ($P = 0.049$). One vertebral and one arm fracture occurred in each group.

### *Graft Outcome*

Graft function at the end of the study was comparable (serum creatinine: ibandronate, 115 ± 40 μmol/L; controls, 142 ± 100 μmol/L; $P = 0.136$). Eleven rejection episodes occurred in the ibandronate group compared with 22 episodes in control subjects ($P = 0.009$; Table 4).

Two patients in the treatment group had early graft loss as a result of renal vein thrombosis (pediatric *en bloc* kidneys). Histology of the explanted kidneys showed no signs of acute rejection. Two patients from the treatment group and three patients from the control group died as a result of infectious complications.

### *Metabolic Data and Side Effects*

Changes in metabolic parameters after transplantation were comparable in both groups (Table 1). Three patients on ibandronate reported side effects in temporal relation to ibandronate administration (bone pain, flatulence). No side effects were reported in the control group. No patient withdrew from the study as a result of side effects.

## Discussion

Significant bone loss occurs subsequent to organ transplantation (2,9,15). Osteopenia is severe in some and tolerable in other patients. Bone loss occurs in cases with normal or low initial bone mineral density. The risk of the individual patient seems to be unpredictable (16). In patients who have received bone marrow, heart, and liver transplants, prophylactic treatment with calcium supplementation (17–19), vitamin D (18–20), calcitonin (17), estrogen, or testosterone (21) has been considered but does not prevent bone loss. Conflicting results were achieved with various bisphosphonates as prophylaxis of posttransplantation osteoporosis. The first-generation compound etidronate could prevent postmenopausal or corticosteroid-induced osteoporosis (10,11) but did not prevent posttransplantation osteoporosis (18,20), probably because of its relative weak potency. Only in the stable phase more than 1 yr after transplantation did patients with already manifest posttransplantation osteoporosis seem to benefit from first-generation bisphosphonates (22,23). The third-generation aminobisphosphonate pamidronate is more potent and seems to be able to prevent the occurrence of posttransplantation osteoporosis (19,24,25). However, all studies done so far were performed without controls or lack power because of the small number of patients. Therefore, we performed a large, prospective, randomized study for prevention of osteopenia after kidney transplantation.

Bisphosphonates are favorable compounds because of the few side effects and efficacy in both genders. They are incorporated into the bone and exert a variety of molecular mechanisms to inhibit osteoclast activity and bone resorption (26). There are various bisphosphonates that demonstrate great differences in their potency, route of administration, and effect on lymphocytes (27). Ibandronate was selected for its high po-

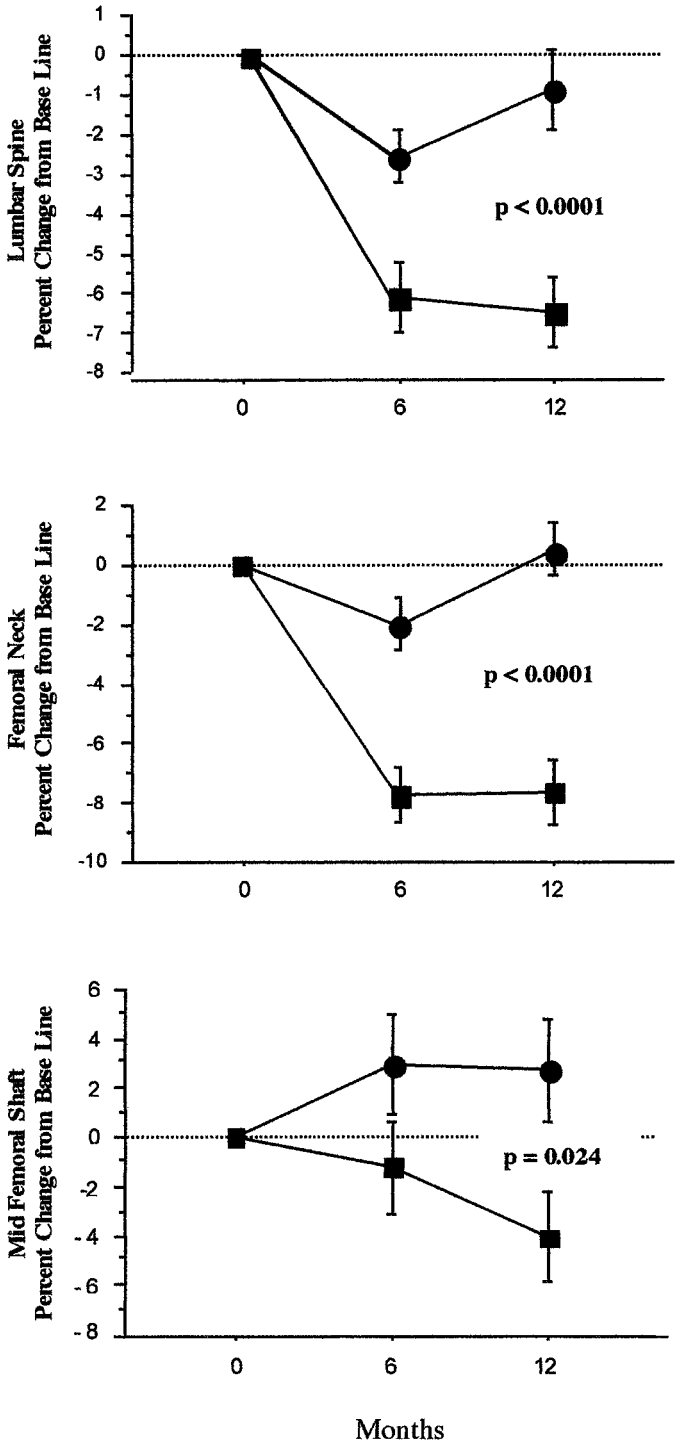


*Figure 2.* Change of bone mineral density in patients with and without ibandronate after kidney transplantation. ●, ibandronate; ■, control.

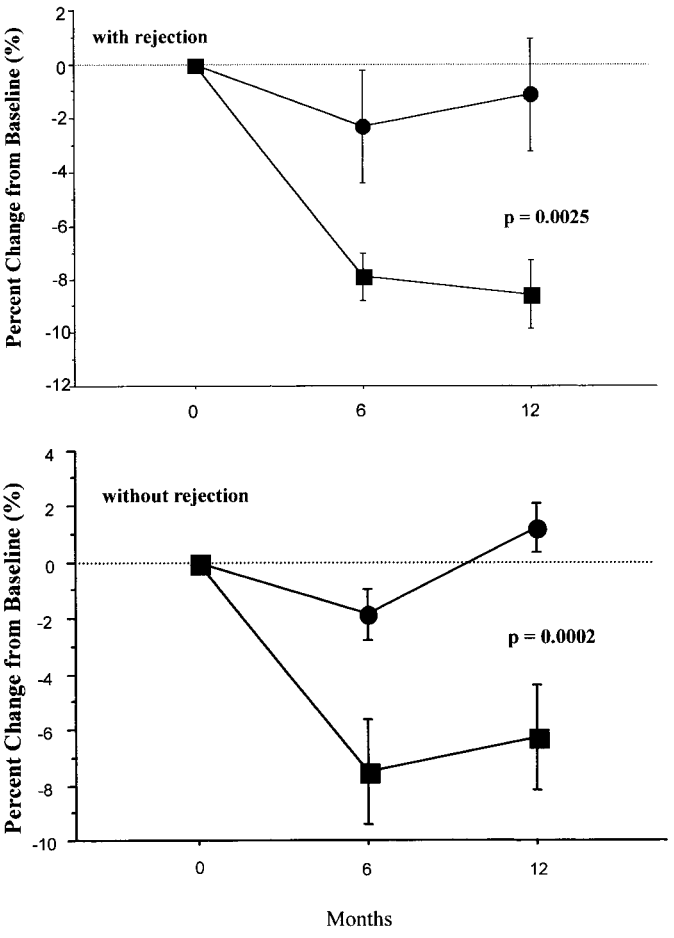


*Figure 3.* Bone loss from baseline at femoral neck in patients with and without rejection. ●, ibandronate; ■, control.

tency and the possibility of intravenous injection. A schedule of four single injections (at transplantation and at 3, 6, and 9 mo thereafter) was used to improve compliance.

In the present study, ibandronate prevented posttransplantation loss of both spongy and cortical bone. Lumbar spine, femoral neck, and midfemoral shaft showed consistent results. Subgroup analysis showed only one possible exception. In the small subgroup of postmenopausal women ($n = 5$), bone loss was seen at lumbar spine but not at femoral neck and midfemoral shaft. It is possible that in these patients, higher doses of ibandronate or addition of estrogen is necessary for inhibition of posttransplantation osteoporosis.

The positive effect of ibandronate on bone mineral density was not accompanied by a reduction of the fracture rate within the 1-yr period. Nevertheless, vertebral deformities were reduced by 70% and decrease of body height by 53% in the ibandronate group. Bisphosphonates have been reported to reduce fracture rate in postmenopausal osteoporosis, which represents a different mechanism of bone loss, however (28,29).

It may be of concern that bisphosphonates aggravate preexistent low-turnover bone disease. In contrast to the situation before transplantation, posttransplantation osteoporosis is a high-turnover bone disease (30,31), making this possibility unlikely. However, bisphosphonates may worsen preexisting hyperparathyroidism (22), which was not observed in the present study. Initial elevated parathyroid hormone levels decreased during the study course and were not different between the ibandronate and control groups.

Interpretation of bone mass change in treatment studies should be done on the background of bone remodeling transient (32,33). The volume of bone involved in remodeling has low bone mineral density. Any drug that inhibits bone remodeling therefore shows an increase of bone mineral density. This apparent increase may be caused by reduction of the remodeling space and not by true biologic gain in bone mass. Because in our study bone mineral density did not decrease after withdrawal of ibandronate, our data reflect a real treatment benefit.

The effect of ibandronate after transplantation could result from reducing initial accelerated bone resorption, when bone formation is low. Our metabolic and bone mineral density data suggest that 6 to 12 mo after transplantation, a new equilibrium between resorption and formation is reestablished since deoxypyridinoline (bone resorption) decreased and bone alkaline phosphatase (bone formation) increased to the normal range during the first year after transplantation. Loss of bone mineral density did slow after 6 mo and showed a continuing, slow bone gain between 12 and 24 mo in both groups. Therefore, it seems that prophylactic treatment of the initial posttransplantation bone loss can be limited to the first year after transplantation. The necessary medication costs of 632 Euros per patient are substantially less than costs of fractures expected in the entire posttransplantation period.

An interesting aspect of our study is the association of reduced incidence of acute rejections and ibandronate treatment. At first glance, this seems surprising and one might suspect a statistical type 1 error. However, there is another explanation. Macrophages play a central role in acute rejection and are still not sufficiently targeted by classical immunosuppressive drugs. Because macrophages and osteoclasts are derived from a common bone marrow progenitor cell, agents that inhibit osteoclasts also inhibit macrophages. Such an immunoinhibitory effect was already shown for alendronate *in vitro*, where it interfered with T-cell function by inhibiting antigen-presenting cells (34). Ibandronate is even more potent than alendronate, and its effects probably are enhanced when given to patients with renal insufficiency in whom the circulating half-life is longer. Other explanations, such as differences of donor–recipient incompatibilities between groups, were excluded. The observation that bisphosphonates are able to reduce incidence of acute rejections is supported by data of various animal studies in which clodronate reduced acute graft rejection after cornea, heart, pancreas, and small bowel transplantation (35–38).

The decreased incidence of rejection episodes in the ibandronate group might have been a potentially confounding variable. Even though not significant, the cumulative dose of corticosteroids was lower in our ibandronate group and could have been responsible for the beneficial effect of ibandronate. This explanation is not supported by a subgroup analysis of patients with and without rejections. Although patients with rejections had received significantly higher cumulative doses of corticosteroids than patients without rejections, ibandronate showed also a clear beneficial effect on bone loss in patients with and without rejection.

Taken together, four injections of ibandronate at 3-mo intervals are sufficient to prevent progression of posttransplantation osteoporosis. A favorable effect of ibandronate on graft tolerance is observed; however, its exact mechanism of action needs to be confirmed in further studies.

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